CLINICAL STUDY PROTOCOL

Phase II trial of IXAZOMIB and Dexamethasone versus IXAZOMIB, Dexamethasone and Lenalidomide, Randomized with NFKB2 rearrangement.

(Proteasome Inhibitor NFKB2 Rearrangement Driven Trial, PINR)

Indication: Relapsed/Refractory Multiple Myeloma
Phase: II

Protocol History

Original DRAFT	6October.2014
Amendment v1.1	12 October 2015
Amendment v1.2	10 June 2016
Amendment v1.3	09 September 2016
Amendment v1.4	28 December 2016
Amendment v 1.5	15 November 2017
Amendment v 1.6	12 March 2020
Amendment v 1.7	09 December 2022

MMRC Lead Investigator and Study Center:

Leon Bernal-Mizrachi, MD (PI)
Sagar Lonial, MD (SubI)
Jonathan Kaufman, MD (SubI)
Ajay Nooka, MD (SubI)
Winship Cancer Institute of Emory University 1365 Clifton Road NE, Bldg. C
Atlanta, Georgia 30322
Telephone: (404) 778-1900
E mail: lbernal@emory.edu

MMRC Participating Academic Investigators and Institutions:

Ravi Vij, MD
Siteman Cancer Center, Washington University in St. Louis

Erica Leigh Campagnaro, MD
University of Michigan

Multi-Site Coordinators for Participating Academic Investigators and Institutions:

Monica Goings, MA
Emory University, Winship Cancer Institute

Phone 404-778-5747
Email: monica.s.goings@emory.edu

Latrisha Moore
Emory University, Winship Cancer Institute
Phone 404-712-0425
E-mail: Latrisha.moore@emory.edu

This is an investigator-initiated study.

PROTOCOL SUMMARY

Study Title: Phase II trial of ixazomib and Dexamethasone versus ixazomib, dexamethasone and lenalidomide, randomized with NFKB2 rearrangement. (Proteasome Inhibitor NFKB2 rearrangement Driven Trial, PINR)

Phase: II

Number of Patients: 90

Study Objectives

Primary

- The primary objective of the study is to test whether the NFKB2 rearrangement can guide the selection of treatment (ixazomib plus dexamethasone (Id) or ixazomib plus lenalidomide and dexamethasone (IRd)) by conducting the 3 following comparison
- To compare the response rate at 4 cycles between non-rearranged NFKB2- patients treated with Id and patients treated with IRd and confirm the lack of significant difference in overall response.
- To compare the response rate at 4 cycles between non-rearranged and rearranged NFKB2 treated with Id and confirm that NFKB2 rearrangement is associated with reduce response rate
- To compare the responses rate at 4 cycles of patients with rearranged NFKB2 treated with Id or IRd and confirm that adding lenalidomide increases the response rate in this population

We assume that adding lenalidomide in the treatment among non-rearranged patients will not further improve the response rate, because our preliminary data allow us to expect that that the response rate of non-rearranged patients with Id will reach 95% and has little room to improve. Therefore, the arm non-rearranged NFKB2 gene treated with IRd has been omitted in order to save resources. Our preliminary data has shown that adding lenalidomide to bortezomib in rearranged NF-kB2 patients, another inhibitor of the proteasome, resulted in response rates of 95% and published phase 1/2 data has shown that oral ixazomib in combination with lenalidomide and dexamethasone in newly diagnosed multiple myeloma achieved a 92% ORR; hence, has little room for improvement either. (Kumar SK et al Lancet Oncology 2014) .

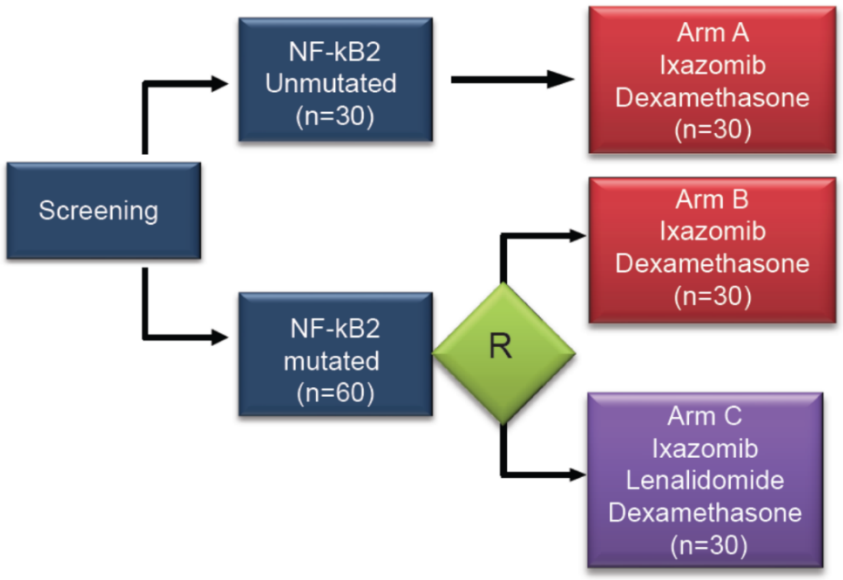
Secondary

- To compare response rates between arms at 8 cycles of treatment
- To determine time to treatment failure (TTF)
- To determine the frequency and severity AE in IRd treated cohort
- To identify novel transcribed mutations associated with Id and IRd resistance in patients with MM.

- To determine the prevalence of NFKB2 rearrangement in Relapsed/Refractory MM patients screened in the study.
- To determine the prevalence of NFKB2 rearrangement according to the type of previous therapies received in all patients screened in the study.
- To determine the toxicity profile of the study drugs according to the presence of NFKB2 rearrangement.
- Delineate transcribed mutations associated with relapse or refractoriness to Id or IRd treatment by RNA-sequencing.

Overview of Study Design:

This is a multicenter open-label, 3-arm, phase II clinical trial to study the differential effect in the treatment efficacy in term of response rate between treatment (Id vs IRd) and plasma cells NFKB2 rearrangement status in relapsed patients with multiple myeloma.
Eligible patients with relapsed MM will be randomized in a 1:1 fashion according to their NFKB2 rearrangement status. Patients without NFKB2 rearrangement will receive ixazomib and dexamethasone. On the other hand, patients with NFKB2 rearrangement will be subsequently randomized in a 2:2 fashion to receive ixazomib and dexamethasone or ixazomib, dexamethasone and lenalidomide. Patients will be administered ixazomib orally at a dose of 4 mg on Days 1, 8, and 15 during a 28-day treatment cycle. Dexamethasone will be administered orally at a dose of 40mg daily on Days, 1, 8, 15 and 22 of a 28 day treatment cycle. In the IRd arm, lenalidomide will be administered orally at a dose of 25 mg daily on Days 1-21. (Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline). Patient without unacceptable toxicity and with at least minimal response should continue treatment until completion of 8 cycles.



Study overview diagram

Patients without NFKB2 rearrangement in their plasma cells will be treated with Id. Patients carrying NFKB2 rearrangement in their plasma cells will be randomized on a 2:2 ratio to either Id or IRd using a randomization table. The study is unblinded and both patient and investigator will know the identity of each patient's study treatment.

Study Population:

Inclusion Criteria:

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting Id (ixazomib and dexamethasone) or IRd (ixazomib, lenalidomide and dexamethasone) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide through 90 days after the last dose of study drug. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 90 days after the last dose of study drug. In the event that the male patients choose to agree to practice true abstinence, this must follow the timelines detailed above. All patients assigned to the lenalidomide treatment group must be registered in and must comply with all requirements of the Revlimid REMS™ program.
4. Multiple myeloma diagnosed according to standard criteria either currently or at the time of initial diagnosis.
5. The patient has confirmed relapsed or refractory MM.
6. For patients that relapse following a response to prior treatment with bortezomib or carfilzomib, six months must have elapsed since the last dose of treatment.
7. The patient has received 1 to 3 prior treatment regimens.
8. Patients must have measurable disease defined by at least 1 of the following

measurements:

- Serum M-protein ≥1.0 g/dL (≥ 10 g/L) for an IgG myeloma, ≥ 0.1 g/dL for an IgD myeloma or 0.5 g/dL (≥ 5g/L) for an IgA myeloma
- Urine light chain ≥ 200 mg/24 hours
- Serum free light chain ≥ 10 mg/dL provided the FLC ratio is abnormal.
- Patients with oligo- or non-secretory disease must have bone marrow involvement with at least 30% plasmacytosis on aspiration.

9. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.

10. Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. In the case that platelets are between 50,000 -75,000, the patient can be enrolled if the plasma cell count in the bone marrow is superior to ≥50%. To meet this hematological eligibility transfusion support are not allowed within 7 days before study enrollment.
- Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.
- Serum creatinine ≤ 2.5 mg/dL or a calculated creatinine clearance ≥ 50 mL/min.

* A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

Exclusion Criteria

1. The patient is refractory to carfilzomib or bortezomib. (Refractory is defined as patients who never achieved a response and progressed while on carfilzomib or bortezomib or within 60 days of completing treatment).

2. Prior treatment with any investigational proteasome inhibitor within 6 months of study entry.

3. Female patients who are breast feeding or have a positive serum pregnancy test during the screening period.

4. Failure to have fully recovered (ie, > Grade 1 toxicity) from the reversible effects of prior chemotherapy.

5. Diarrhea > Grade 1 according to NCI CTCAE v4.03

6. Prior chemotherapy and/or immunotherapy within 14 days before enrollment. Major surgery within 14 days before enrollment and minor surgery within 7 days prior to Cycle 1 Day 1

7. Radiotherapy within 14 days before enrollment. If the involved field covered ≤ 5% of the bone marrow reserve, the patient may be enrolled irrespective of the end date of radiotherapy.

8. Central nervous system involvement.

9. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

11. Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

12. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

13. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially compromise the patient's ability to understand the patient information, to give informed consent, to comply with the treatment according to this protocol or complete the study.

14. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual

disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

15. Patient has ≥ Grade 2 peripheral neuropathy or neuropathy with pain, regardless of grade that is seen on clinical examination during the screening period.

16. Known intolerance to IMiDs.

17. History of allergic reaction/hypersensitivity to any of the study medications, their analogues or excipients in the various formulations.

18. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or lenalidomide, including difficulty swallowing.

19. Participation in other clinical trials, including those with other investigational agents not included in this trial, such as monoclonal antibodies, within 30 days of the start of this trial and throughout the duration of this trial.

20. Corticosteroid doses > 10 mg/day of prednisone or equivalent within 14 days prior to Cycle 1 Day 1.

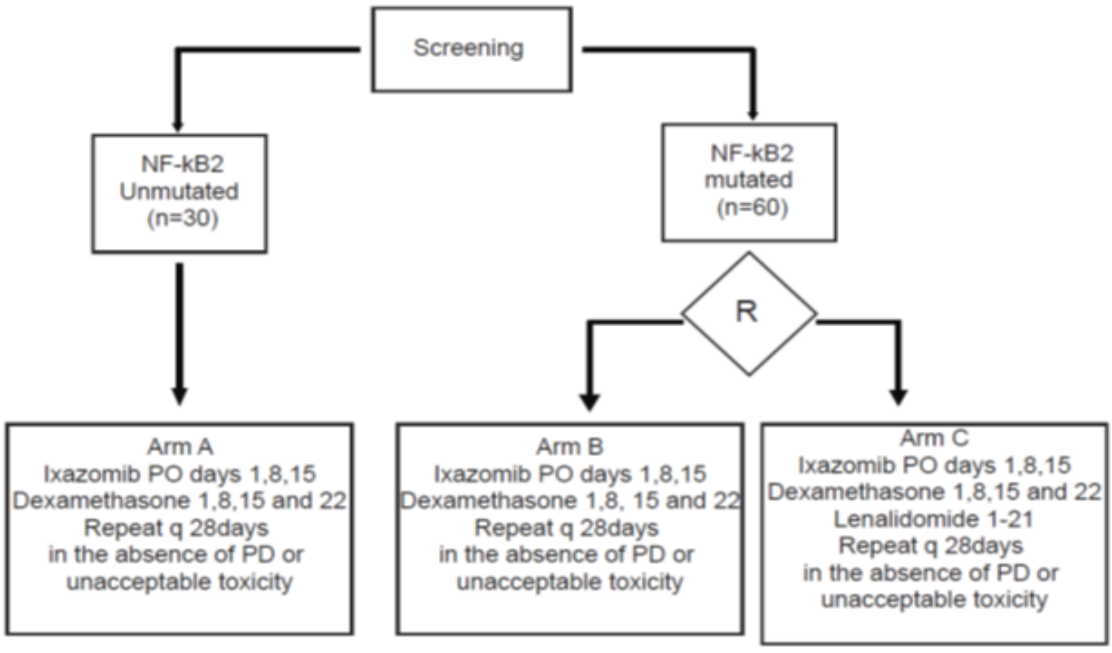
21. Autologous or allogeneic stem cell or bone marrow transplant within 3 months prior to Cycle 1 Day 1.

22. Cytotoxic therapy within 21 days prior to Cycle 1 D1

23. Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not.

Duration of Study: The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period may continue until disease progression, unacceptable adverse reaction or other reason for discontinuation. After study treatment discontinuation an end of treatment (EOT) visit will be done at 30 days to assess safety. Patients who discontinue treatment for reasons other than progression of disease will be followed monthly until progression or initiation of subsequent therapy.

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

PROCEDURES	Screen	Cycle 1 Each cycle is 28 days				Cycle 2-8 Each cycle is 28 days				Cycle 9+ Each cycle is 28 days	End of Treatment	Post Study Follow Up
	-21d to -1d	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day1		
Window		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1			
Informed Consent	X											
Medical History, Demographics	X											
Concomitant Medications	X	X		X		X				X	X	
PE, Height[1], Weight, ECOG	X	X				X				X	X	
Toxicity Evaluation		X				X				X	X	
Vital Signs (HR, Temp, BP)	X	X				X				X	X	
12-lead ECG[3]	X											
CBC with differential[4]	X	X		X		X				X	X	
Serum Chemistry[5]	X	X		X		X				X	X	
Microscopic Urinalysis	X											
Neurological exam (FACT/GOG Ntx)[6]	X					X				X	X	
PT/PTT	X											
TSH	X											
Pregnancy test [FCBP] [2] (serum or urine)	X	X	X	X	X	X		X[2]		X		
Extramedullary disease[7]	X										X	
Skeletal Survey [8]	X									X[8]	X	
Bone Marrow Aspiration/Biopsy[9]	X									X[9]	X	
Myeloma-specific lab tests[10]	X					X				X	X	X
Blood for correlative labs[11]	X					X					X	

PROCEDURES	Screen	Cycle 1 Each cycle is 28 days				Cycle 2-8 Each cycle is 28 days				Cycle 9+ Each cycle is 28 days	End of Treatment	Post Study Follow Up
	-21d to -1d	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day1		
ixazomib Administration		X	X	X		X	X	X		Days 1, 8, 15		
Dexamethasone		X	X	X	X	X	X	X	X	Days 1, 8, 15, 22		
Lenalidomide Administration (IRd arm only)		Days 1 – 21 IRd Arm only				Days 1 – 21 IRd Arm only				Days 1 – 21 IRd Arm only		
Follow for PD and survival												X[12]

1. Measured at screening only.
2. ARM A and B: FCBP on this arm will not be taking lenalidomide. Females of reproductive potential in these arms must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to the first dose of ixazomib. A pregnancy test will be performed at day one on all future cycles or every 14 days if she has irregular menstruation. ARM C: This arm will be taking lenalidomide. FCBP must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide and ixazomib. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of lenalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of lenalidomide. * FCBP - A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.
3. ECG (12-Lead) should be performed at screening and read locally.
4. CBC to be performed and reviewed by clinician within 24 hours of day of dosing (first day of each cycle), on Day 15 of Cycle 1 and more frequently if clinically indicated. Alternately, a STAT CBC may be drawn on day of dosing however should be reviewed prior to administration of investigational product(s).
5. Serum Chemistry to be performed and reviewed by the investigator within 24 hours of day of dosing (first day of each cycle). Alternately, a STAT CMP may be drawn on day of dosing however should be reviewed by the investigator prior to administration of investigational product(s). Chemistry includes: glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, BUN, creatinine, ALP, ALT, AST, bilirubin, uric acid, magnesium, phosphorus, LDH. Weight and serum creatinine will be used to calculate creatinine clearance by Cockroft-Gault equation (see appendix 16.2).

6. FACT GOG NTx: Neurological assessment required at screening and Day 1 of Cycle 2+. Results should be compared with prior assessment for the presence of peripheral neuropathy or other neurotoxicity.
7. Extramedullary Disease: Assess by physical exam and/or radiologic evaluation as clinically indicated. Disease that can be assessed by physical exam should be evaluated on Day 1 of each cycle. Disease that can be assessed by radiologic evaluation should be assessed according the IMWG criteria for evaluation of response. This may include computerized tomography (CT) scan, ultrasound, positron emission tomography [PET]/CT or MRI. The same method of assessment should be used at each evaluation
8. Skeletal survey (including skull, all long bones, pelvis and chest) with tumor measurements if plasmacytomas present. Also required if previous survey >28 days from study entry and at any time when clinically indicated to confirm progression according to IMWG criteria. Subjects should repeat the skeletal survey at minimum every 12 months as SOC, or as clinically indicated.
9. A bone marrow biopsy and aspiration is required at screening for cytogenetic analysis by fluorescence in situ hybridization (FISH), standard karyotyping, % plasma cells, morphology, NFKB2 rearrangements and correlative studies. Repeat bone marrow aspirate if CR (at any time during study participation), at relapsed, or at progression, stringent complete response (sCR) is suspected to confirm achievement of response according to IMWG criteria and End of therapy.
10. Myeloma lab tests: β2 Microglobulin at baseline, serum and 24 hours urine immunoelectrophoresis, serum immunoglobulin assay, Serum/urine immunofixation and serum free light chain with kappa/lambda ratio to be performed at baseline, every cycle prior to study treatment administration thereafter and at end of treatment (if last tests were > 4 weeks) and for patients who discontinue therapy for reasons other than progression, MM labs will be repeated every month until progression or initiation of subsequent therapy. Response assessment will be done at the beginning of every cycle.
11. One 5-mL blood sample will be collected during screening or on Cycle 1, Day 1 before the first dose of Id or IRd is administered to assess potential biomarkers that predict response to Id vs IRd. One 5-mL blood sample will be collected on Cycle 4 Day 1 and One 5-mL blood sample will be collected at progression. If progression/relapse occurs before Cycle 4, then only the progression sample is needed. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.
12. After study treatment discontinuation an end of treatment (EOT) visit will be done at 30 days to assess safety. Patients who discontinue treatment for reasons other than progression of disease will be followed monthly until progression or initiation of subsequent therapy.

*Additional tests to be performed at the beginning of each cycle and at any reasonable time point during treatment if indicated for monitoring of drug profile/safety or, for disease/health status at the discretion of the clinical investigator.

TABLE OF CONTENTS

59

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CV	cardiovascular
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EBMT	European Group for Bone and Bone Marrow Transplant
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
HIV	human immunodeficiency virus
IB	Investigator's Brochure

Abbreviation	Term
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MSC	multi-site coordinator
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
RBC	red blood cell
sCR	stringent complete response
SAE	serious adverse event
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
ULN	upper limit of the normal range
US	United States
VD	Bortezomib dexamethasone
VGPR	very good partial response

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Multiple Myeloma

Multiple myeloma is a heterogeneous malignancy characterized by the accumulation of terminally differentiated antibody secreting B cells that result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. In the United States (US), multiple myeloma represents the second most common hematological malignancy with approximately 5 to 7 new cases diagnosed per 100,000 people each year. Approximately 20,000 cases of multiple myeloma are diagnosed each year and 11,000 deaths per year are due to the disease (approximately 2% of all cancer deaths) and these rates are similar to those seen in Europe. [1]

Although multiple myeloma is uniformly fatal, treatment has dramatically improved over the last several decades because of the use of cytotoxic drugs, the introduction of high dose therapy and autologous transplant, and the development of novel agents. Five-year survival has improved from 25% in 1975 to 34% in the period from 1999 to 2005 because of the development of more effective treatment. [2,3] Most patients receive multiple therapies over the course of their disease; however, responses are transient despite the marked improvement in treatment options. Multiple myeloma is sensitive to a number of cytotoxic drugs such as alkylating agents, anthracyclines, and corticosteroids for initial treatment and for relapsed disease. With the introduction of several effective agents such as proteasome inhibitors (bortezomib), thalidomide, and lenalidomide, the treatment response and the 5-year survival of multiple myeloma has improved.

1.1.2 Risk stratification in Multiple Myeloma.

The completion of the sequencing of the MM human genome and many genomic studies confirmed multiple molecular entities that differ in clinical outcome.[4] The completion of these studies have been accompanied with the approval of many new drugs, but in contrast to other tumors, these technologies have been unable to identify a companion diagnostic test that predict the subset of patients that would benefit from specific therapies. As a result much effort has been dedicated to define relevant MM molecular categories that will predict a successful outcome. As such, the use of genetic approaches (like t(4-14), t(14-16) or chromosome 13 deletion or inactivation of p53, etc), clinical risk categories (International Staging System Grade III), biological markers (high proliferation rate), and gene expression analyses (FGFR3/MMSET, MAF, cyclin D, hyperdiploid) have been developed to identify patients with high risk disease. However, none of these technologies affect the selection of initial therapeutic combinations,

making it difficult to justify for some of them their constant clinical application. Therefore, standard regimens are applied to all patients without scrutinizing for biological characteristics that could determine the intensity of the therapy required to achieve an optimal response.

1.2 Clinical Experience With Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma.

Revlimid (lenalidomide) is a thalidomide analogue that has significant clinical activity in multiple myeloma. Lenalidomide in combination with dexamethasone is approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma patients who have received at least 1 prior therapy. [5, 6] Based on the activity of this combination in the relapse/refractory setting, clinical trials are ongoing or have been completed in patients with NDMM. [7]

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase 3, multicenter, open-label study (E4A03) in patients with NDMM. The primary outcome of the trial was to determine whether low-dose dexamethasone plus lenalidomide was noninferior to high-dose dexamethasone plus lenalidomide. After 4 cycles of therapy, patients could either discontinue the planned protocol therapy to undergo a stem-cell transplant or continue on protocol therapy until disease progression. [7] Results suggest that that lenalidomide plus low-dose dexamethasone is associated with better OS and a lower toxicity profile compared to lenalidomide plus high-dose dexamethasone. [7] In this study, 445 patients were randomly assigned to a high-dose (n = 223) or low-dose (n = 222) dexamethasone/lenalidomide regimen. Patients randomized to the high-dose regimen were administered lenalidomide 25 mg on Days 1 through 21, plus dexamethasone 40 mg on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients assigned to the low-dose regimen received the same schedule of lenalidomide with dexamethasone 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle.

One hundred and sixty-nine (79%) of 214 patients receiving high-dose treatment and 142 (68%) of 205 patients on low-dose treatment had complete response (CR) or partial response (PR) within 4 cycles. At the 1-year, second interim analysis, however, OS was 96% (95% confidence interval 94–99) in the low-dose dexamethasone group compared with 87% (82–92) in the high-dose group ($p = 0.0002$). The most common Grade 3 toxicities were deep vein thrombosis (26% vs 12%; $p = 0.0003$), infections including pneumonia (16% vs 9%; $p = 0.04$), and fatigue (15% vs 9%, $p = 0.08$) for the high-dose vs low-dose dexamethasone containing groups respectively. Consequently, the trial was stopped and patients on high-dose therapy were crossed over to low-dose therapy. [7]

The Southwest Oncology Group (SWOG) conducted a randomized, phase 3, double-blind, crossover, placebo-controlled, multicenter study in patients with NDMM. [8] The primary endpoint was to compare the progression-free survival (PFS) of patients treated with dexamethasone plus lenalidomide or placebo. The target accrual was 500 patients; however the study closed early with an accrual of 198 after results of the ECOG trial E4A03 reported improved survival using low-dose dexamethasone versus high-dose dexamethasone plus lenalidomide. [8] These results affected the acceptability of the high-dose dexamethasone control group.

In a blinded manner, patients participating in the SWOG trial were randomized to lenalidomide 25 mg on Days 1 through 28 of a 35-day cycle for 3 induction cycles, then 21 of 28 days as maintenance, plus dexamethasone 40 mg on Days 1 through 4, 9 through 12, and 17 through 20 in induction, and then on Days 1 through 4, and Days 15 through 18 during maintenance; the comparator arm included dexamethasone plus placebo administered according to the same induction and maintenance schedules. Therapy was unblinded at disease progression and patients in the control arm could cross over to the lenalidomide-dexamethasone regimen. The estimated 1-year PFS was 77% in the 100 patients treated with lenalidomide-dexamethasone and 55% in the 98 with dexamethasone plus placebo; however, 1-year OS was similar in both groups (93% vs 91%).[8] The response rate was 85.3% (22.1% CR) versus 51.3% (3.8% CR) in the groups respectively. Grade ¾ neutropenia, infections, and thrombosis were more common in patients treated with lenalidomide-dexamethasone.

1.3 Multiple Myeloma and Response to Proteasome Inhibitor.

Protein homeostasis that occurs through regulation of protein production and destruction is one of the critical biological processes that play a role in cell survival. The ubiquitin-proteasome system is the major regulatory system through which this occurs and represents the primary mechanism by which cells degrade proteins, including those involved in growth control, cell cycle regulation, and apoptosis.

The completion of these biological studies has allowed the development of several new potent drugs in MM1. One such medication, the proteasome inhibitor, has become the backbone of current therapeutic approaches for MM. These drugs inhibit the catalytic proteolytic core (20S) subunit of the 26S proteasome. As a consequence proteasome inhibitors reduced protein degradation and disrupt several distinct cell regulatory mechanisms leading to inhibition of cell growth and survival pathways, dysregulation of the cell cycle, and induction of apoptosis. Clinical studies with the only FDA approved proteasome inhibitor, bortezomib, have validated the proteasome as a therapeutic target for the treatment of malignancies. Bortezomib is approved for

the treatment of patients with multiple myeloma and previously treated mantle cell lymphoma. (Bortezomib product label)

Bortezomib has proven effective in the frontline setting, has shown marked response in the relapsed setting, and is an effective agent in the pretransplant setting. However, 38% of the patients treated with the first generations of bortezomib combination (dexamethasone) achieved optimal response (defined as complete or very good response), 60%-87% of patients fail to reach this goal 2. Hence, second generation of bortezomib combinations including other novel agents have been develop and are achieving significant improvements in its therapeutic response (OR:70-90% with complete responses in 40-50% of the cases) and overall survival (of 29-35% at 5 years) 3. But, despite the marked increase in the number of therapeutic options, the disease remains incurable and there remains a need for new and better agents. Hence new efforts to target the 20S proteasome has allowed the dosing of second-generation proteasome inhibitor (Ixazomib) for the treatment of both hematologic and non-hematologic malignancies.

1.4 Clinical Experience of BORTEZOMIB [Bortezomib] Plus Lenalidomide and Dexamethasone.

Evidence to support combining bortezomib with immunomodulatory analogues, includes preclinical data demonstrating synergistic effects on apoptosis, clinical efficacy seen with the combination of bortezomib, lenalidomide, and dexamethasone in relapsed/ refractory disease, and the clinical activity of these agents in NDMM patients. [11-16].

Richardson and colleagues conducted a phase 1/2 study combining lenalidomide, bortezomib, and dexamethasone in NDMM patients. [11] The primary endpoints were to determine the maximum tolerated dose (MTD) of this combination (phase 1) and to evaluate response rate (≥PR) to the combination (phase 2). Response assessments were done after 4 and 8 cycles of therapy. Responses were assessed by modified European Group for Bone and Bone Marrow Transplant (EBMT) and Uniform criteria [17] to include near complete response (nCR) and very good partial response (VGPR). Patients received lenalidomide on Days 1 through 14, bortezomib on Days 1, 4, 8, and 11, and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12, for eight 21-day cycles. Patients with a CR or nCR/PR after Cycle 4 could proceed at any point to stem cell mobilization and transplantation. Patients with stable or responding disease without unacceptable toxicity at the completion of Cycle 8, were allowed to continue onto the maintenance phase of the study which comprised 3-week cycles of bortezomib on Days 1 and 8, lenalidomide on Days 1 through 14 at the doses tolerated at the completion of Cycle 8, and dexamethasone 10 mg the day before and after bortezomib (Days 1, 2, 8, and 9). [11]

In the phase 1 portion of the study, dose-escalation proceeded (3 patient cohorts) depending on dose-limiting toxicities (DLTs) initially with 4 planned dose levels (lenalidomide/bortezomib: 15/1.0, 15/1.3, 20/1.3, 25/1.3 plus dexamethasone at fixed doses of 40 mg cycles 1-4 /20mg cycles 5-8). Based on safety data, an additional dose level (ie, 4M [lenalidomide 25mg/bortezomib1.3 mg/m^2]) with reduced dexamethasone (20/10 mg), was added; this was determined to be the MTD of the combination and the recommended phase 2 dose (RP2D). Overall 66 patients were enrolled to this study (phase 1 n = 31; phase 2 n = 35). [11]

Results indicated that the combination of lenalidomide, bortezomib, and dexamethasone was highly active in patients with NDMM, with all patients (100%) achieving at least a pre-ASCT response of PR and high rates of VGPR or better (CR+ nCR+VGPR). Consistent with reports from other studies, response rates were unaffected by adverse cytogenetic abnormalities. In both the phase 2 population and overall, 74% and 67% respectively achieved a VGPR or better. Overall, 49 patients achieved at least a PR after 4 cycles of treatment (6% CR/nCR; 5% VGPR, and 64% PR). Improvement in response by at least one response category was noted in 75% of the 56 patients that continued on therapy from Cycle 4 through Cycle 8, with further improvement in response noted in 20 of 37 patients who continued beyond cycle 8 with maintenance therapy. With a median follow-up of 21 months, neither the median duration of response (DOR) nor median OS has been reached. With 68% of patients still responding after more than 18 months, the estimated 18-month PFS and survival with/without ASCT is 75% and 97% respectively. The 3-drug combination was well tolerated with generally manageable toxicities. Neuropathy was noted but often low grade and reversible with dose modification. There was no Grade 4 neuropathy and limited rates of Grade 3 neuropathy (2% peripheral sensory neuropathy [any grade 80%], 2% peripheral motor neuropathy [any grade 18%], and 3% neuropathic pain [any grade 32%]). Other Grade 3 or 4 toxicities reported in at least 5% of patients included lymphopenia (14%), neutropenia (9%), thrombocytopenia (6%), thrombosis (6%), hypokalemia (5%), and hypophosphatemia (5%). [11] The authors concluded the bortezomib, lenalidomide, dexamethasone (VRD) combination was a highly effective regimen for patients with NDMM supporting the ongoing phase 3 clinical trials designed to assess the benefit of this 3-drug approach compared with a 2-drug approach (dexamethasone plus either bortezomib or lenalidomide, depending on the specific trial). [11]

Kumar and colleagues reported results of a randomized, phase 1/2 study of 3- and 4-drug combination regimens containing bortezomib (BORTEZOMIB; V), dexamethasone (D), lenalidomide (Revlimid, R), with or without cyclophosphamide (C) in subjects with NDMM

(EVOLUTION Study). [12] Previously untreated patients with measurable disease were randomized to 1 of 4 treatment groups receiving up to eight 21-day cycles of induction therapy followed by four 42-day maintenance cycles of V 1.3 mg/m2 (Days 1, 8, 15, 22) (all treatment arms). Patients eligible for autologous stem cell transplant could undergo stem cell mobilization any time after cycle 2 and stem cell transplant (SCT) any time after Cycle 4. Response categories were based on the IMWG Criteria (See section 15.3) with the addition of nCR, and adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. The phase 1 part of the study evaluated increasing doses of cyclophosphamide with fixed doses of bortezomib, dexamethasone, and lenalidomide in order to determine the MTD of the combination. [12] The primary endpoint of the Phase 2 portion of the study was the combined CR + VGPR rate. All combinations administered bortezomib 1.3 mg/m2 IV (Days 1, 4, 8, 11) and dexamethasone 40 mg orally (Day 1, 8, 15) every 21 days repeated for 8 cycles followed by bortezomib 1.3 mg/m2 alone (Days 1, 8, 15, 22) in a 6-week cycle for 4 cycles. Revlimid was given at 25 mg orally (Days 1-14) in the VDR arm and at 15 mg in the VDCR arm. In the VDCR arm, patients were treated with escalating doses of cyclophosphamide (100, 200, 300, 400, or 500 mg/m2) orally Days 1, 8, and every 21 days. As previously reported, the recommended phase 2 dose of cyclophosphamide in the VDCR regimen was the highest planned dose of 500 mg/m2. [13] In the phase 2 part of the study, the VDC arm was modified to add a Day 15 dose of cyclophosphamide given the lower than previously reported efficacy rate of the VDC combination.

One-hundred forty patients were enrolled with 132 patients being response evaluable (42 VDCR, 42 VDR, 32 VDC, and 17 VDC-modified) at the data cut-off. Responses and estimated long-term outcomes are noted below in Table 1-1. The median number of VDR, VDCR, VDC, and VDC-modified cycles received is 5 (range 1-12), 6 (range 1-12), 6 (range 3-12), and 6 (range 3-12), respectively. The median DOR had not been reached in any arm as of the data cut-off. Forty-six patients had samples assessed for minimal residual disease with 46% of those who achieved CR (including stringent CR [sCR]) or nCR being minimal residual disease-negative. [13]

Table 1-1. Best confirmed response

Response %	VDCR	VDR	VCD	VCD-mod
ORR (> PR) (%)	88	83	78	100
CR	24	24	22	47

sCR	10	14	3	29
CR + nCR	34	38	31	47
≥ VGPR	59	50	41	59
≥ nCR pts with MRD negative % (# MRD negative/# assessed).	48 (10/21)	75 (9/12)	0 (0/7)	33 (2/6)
1 Year PFS, %	82	68	97	100
Survival at 1 yr/ 2 yrs, %	92/76	100/96	100/100	100/NE

Source: Kumar S, Flinn I, Richardson P, Hari P, Callander N, Noga S, et al. [13] Novel Three- and Four-Drug Combination Regimens of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide, for Previously Untreated Multiple Myeloma: Results From the Multi-Center, Randomized, Phase 2 EVOLUTION Study. Blood (ASH Annual Meeting Abstracts) 2010;116(21):abstr 621. [13] Abbreviations: C = cyclophosphamide; CR = complete response; D = dexamethasone; MRD = minimal residual disease; N = number; nCR = near CR; PFS = progression-free survival; PR = partial response; R = Revlimid (lenalidomide); sCR = stringent CR; V = Velcade (bortezomib). a Censoring at transplant.

All treatment regimens were generally well tolerated. The five most common all-grade AEs across all treatment groups were fatigue (range 47%–67%), nausea (36%–67%), constipation (40%–62%), diarrhea not otherwise specified (42%–65%), and neutropenia (19%–52%). The incidence of Grade >2 neuropathy was similar across each arm with no reports of Grade 4 peripheral neuropathy (Table 1-2).

Table 1-2. Selected Adverse Events

AE %	VDCR (n=41)	VDR (n=42)	VCD (n=32)	VCD-mod (n=17)
> G3 AE	81	76	79	88
SAE	42	40	21	41
AE resulting in study discontinuation	19	17	12	6
Peripheral Neuropathy	34	38	31	47
>G2 (>G3)	40(13)	45 (14)	48 (9)	41 (18)
Neutropenia (>G3)	42	7	36	65
Thrombocytopenia > G3	82	68	97	100
Survival at 1 yr/ 2 yrs, %	10	7	12	18

Source: Kumar S, Flinn I, Richardson P, Hari P, Callander N, Noga S, et al. [13] Novel Three- and Four-Drug Combination Regimens of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide, for Previously Untreated Multiple Myeloma: Results From the Multi-Center, Randomized, Phase 2 EVOLUTION Study. Blood (ASH Annual Meeting Abstracts) 2010;116(21):abstr 621. [13] Abbreviations: AE = adverse event; C = cyclophosphamide; D = dexamethasone; Gr = grade; N = number; R = Revlimid (lenalidomide); SAE = serious AE; sCR = stringent CR; V = VELCADE (bortezomib).

The authors concluded that VDR, VDCR, and VDC (initial and modified) are highly active in patients with NDMM. The regimens are well tolerated with modest increase in hematologic toxicity (ie, Grade 3/4 neutropenia) in the cyclophosphamide-containing regimens. The VDC-mod regimen was associated with high and rapid responses comparable to VDR and VDCR. Long-term follow-up continues to assess the durability of response as well as the depth of the response. [13]

SWOG is currently conducting a randomized, phase 3 trial of lenalidomide with low-dose dexamethasone (LLD) versus bortezomib plus LLD for induction in patients with NDMM without intent for immediate autologous stem cell transplant (S0777). The primary outcome of the trial is to compare PFS with LLD with or without bortezomib. A secondary objective is to assess OS and long-term outcomes stratified by intent to undergo transplantation at progression. Patients are randomized to lenalidomide 25 mg on Days 1 through 21 plus dexamethasone 40 mg on Days 1, 8, 15, 22, and every 28 days for 6 cycles or to bortezomib 1.3 mg/m2 on Days 1, 4, 8, and 11 plus dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 with lenalidomide 25 mg on Days 1 through 14 every 21 days for 8 cycles. Patients whose disease progresses or who experience unacceptable toxicity are removed from the study at that time. After 6 months of therapy, patients without progressive disease (PD) or unacceptable toxicity receive maintenance therapy consisting of dexamethasone 40 mg on Days 1, 8, 15, and 22 with lenalidomide 25 mg on Days 1 through 21 every 28 days. Maintenance continues until disease progression or unacceptable toxicity. In both arms, patients who intend to undergo SCT may undergo collection of stem cells after 2 cycles of therapy with the ASCT at relapse. The trial began accrual in April 2008 with a target of 440 patients.

1.5 Ixazomib

1.5.1 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.5.2 Clinical Experience

Ixazomib has been evaluated as an oral single agent in Phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring

systemic treatment, 2 Phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions (DDI) with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthemas NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%),

decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.5.3 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days [6]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [7]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is

administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

1.5.4 Clinical Trial Experience Using the Oral Formulation of ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 1-1 Clinical Studies of Oral ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment

C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W

Table 1-1 Clinical Studies of Oral ixazomib

Trial/ Population	Description	Doses Investigated
C16014 Symptomatic MM N=701	PO, combination with LenDex	Ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: Ixazomib 3.0 mg on Day 1 Part B: Ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle

C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA= body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

1.5.5 Overview of the Oral Formulation of ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all Phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash maculara	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: ixazomib Investigator's Brochure Edition 7
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.
a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Edema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash..

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [7], non-Hodgkin's disease, Hodgkin's disease [8], relapsed and/or refractory multiple myeloma [RRMM; 9-17], relapsed or refractory systemic light chain amyloidosis [RRAL; 12], and newly diagnosed multiple myeloma [NDMM; 13-15]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.5.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and

C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, Phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(15, 16) Study C16004 is an open-label, dose escalation, Phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.(17, 18, 19) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Ixazomib trial C16003 a Phase 1 study of twice-weekly dosing of investigational oral proteasome inhibitor ixazomib in patients with relapsed and/or refractory multiple myeloma(21). Among 55 response-evaluable patients, 15% achieved partial response or better (with 76% stable disease or better). These findings have informed the subsequent clinical development of ixazomib in multiple myeloma.

In trial C16004, weekly dosing of ixazomib in relapsed/refractory multiple myeloma (22), the MTD was determined to be 2.97 mg/m . Dose-limiting toxicities were grade 3 nausea, vomiting, and diarrhea in 2 patients, and grade 3 skin rash in 1 patient. Common drug-related adverse events were thrombocytopenia (43%), diarrhea (38%), nausea (38%), fatigue (37%), and vomiting (35%). The observed rate of peripheral neuropathy was 20%, with only one grade 3 event reported. Nine (18%) patients achieved a partial response or better, including 8 of 30 (27%) evaluable patients treated at the MTD. Pharmacokinetic studies suggested a long terminal half- life of 3.6-11.3 days, supporting once-weekly dosing.

1.5.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with

similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

The C16005 trial evaluated the combination of weekly MNL9708 and lenalidomide in a phase 1/2 trial. Of 19 response-evaluable pts (Ph 1 + Ph 2), all achieved ≥PR, including 5 CR (1 sCR), 4 VGPR, and 10 PR; all remain in response with duration of confirmed response of up to 9.5 months. Of 4 response-evaluable Ph 2 pts, 1 has achieved VGPR and 3 PR to date. Oral ixazomib plus lenalidomide and dexamethasone appears well tolerated with manageable toxicity. These data show antitumor activity at the RP2D in pts with previously untreated MM, with ≥PR in all patients at the time of reporting (ref).

Twice-weekly oral ixazomib in combination with lenalidomide (len) and dexamethasone (dex) in patients with newly diagnosed multiple myeloma was also reported.(23) In 58 response-evaluable pts, ≥PR rate to date was 93%, including 67% ≥VGPR (24% CR, including 14% sCR). 54% of pts had 100% decreases in M-protein or serum free light chain from baseline. Analysis of minimal residual disease is ongoing; data will be presented. Depth of response increased over the course of treatment; median time to first response (≥PR) was 0.69 mos and to best response to date was 2.07 mos. Median DOR to date was 5.9+ mos, ranging up to 18+ mos. Most common AEs were rash (61%; pooled high-level terms), fatigue, peripheral edema (each 50%), diarrhea (41%), and neuropathy peripheral (36%). Drug-related (to any drug in the regimen) grade 3 AEs were seen in 56% of pts, including rash (16%), hyperglycemia (8%), pneumonia (6%), and PN (5%; high- level term). No drug-related grade 4 AEs were seen; 58% of pts required dose reductions of at least one drug due to AEs including rash (16%), anxiety (11%), and PN (8%). AEs resulting in discontinuation were seen in 11%, with the majority reported as not related to therapy. There was 1 on-study death due to cardio-respiratory arrest, likely a pulmonary embolism, considered by the investigator to be unrelated to ixazomib or dex, but probably len. Based on phase 1 preliminary PK data, MLN2238 was absorbed quickly with a Tmaxof 0.5–4 hours. Terminal half-life was 2–8 days. PK data were similar to single-agent twice-weekly dosing studies, suggesting no MLN2238 PK interaction with len or dex.

These data suggest that twice-weekly oral ixazomib plus len-dex is feasible and active in pts with newly diagnosed MM. However, rates of rash, PN, and dose reductions appear higher than in the parallel study using weekly ixazomib, with similar response rates and better convenience, supporting use of weekly dosing in ongoing phase 3 trials and future combination trials such as this one.

All 3 studies are Phase 1/2, with Phase 1 focusing on safety and Phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.5.8 Clinical Trial Experience Using the Intravenous Formulation of ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.6 NFKB2 Biomarker

A prospective study between May 2007 to June 2012 was performed to analyze the loss of NFKB2 3'end in patients treated with Bortezomib and Dexamethasone (VD). The outcome of the study was to determine if the loss of NFKB2 was associated with suboptimal (defined as stable or progressive disease) response at 4 cycles. In this study 83 patients were recruited. Twenty seven ineligible patients were excluded from the study because they had a treatment variation (n=15), misdiagnosis (n=2), poor quality of bone marrow sample (n=3), low quality sorting (n=5) or extra medullary disease only (n=2). Thus, clinical information, plasma cells and match germ line DNA derived from blood granulocytes was obtained from 56 patients. Patient characteristics at inclusion are shown in Table 1 (appendix 1). Twelve patients (21%) with impaired renal function (serum creatinine more than 1.5 mg/dL) were included.

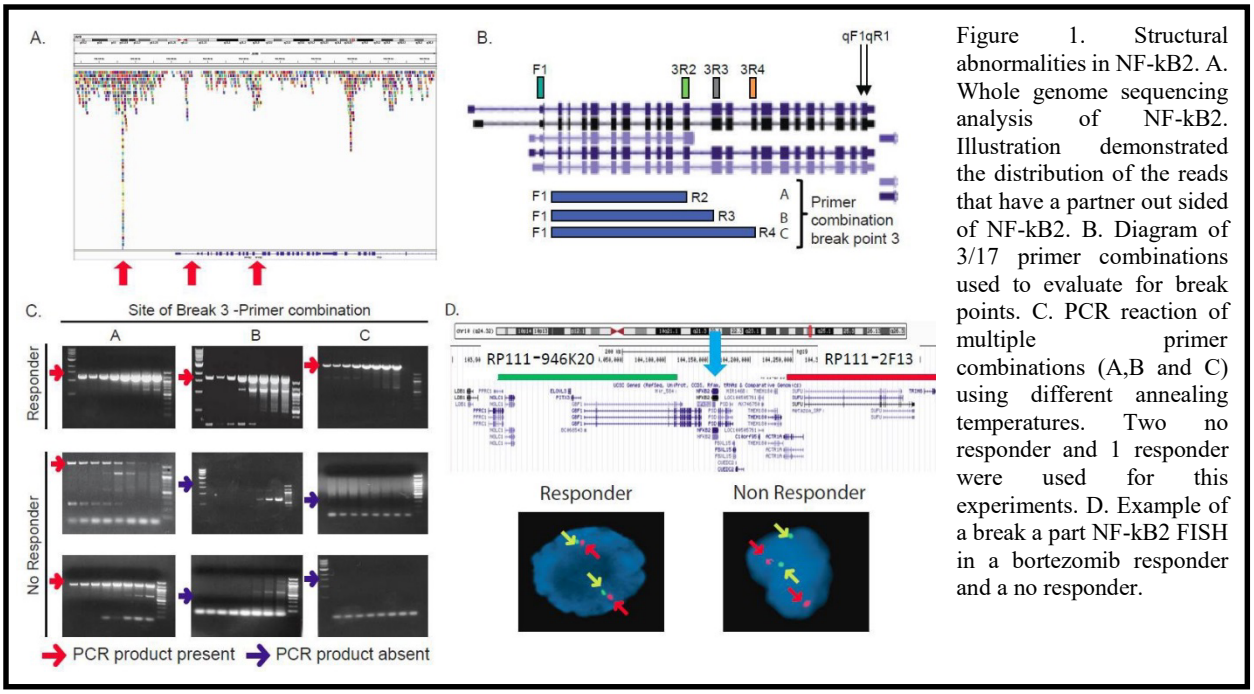


Figure 1. Structural abnormalities in NF-kB2. A. Whole genome sequencing analysis of NF-kB2. Illustration demonstrated the distribution of the reads that have a partner out sided of NF-kB2. B. Diagram of 3/17 primer combinations used to evaluate for break points. C. PCR reaction of multiple primer combinations (A,B and C) using different annealing temperatures. Two no responder and 1 responder were used for this experiments. D. Example of a break a part NF-kB2 FISH in a bortezomib responder and a no responder.

In this population, 40 patients (70%) had available results from FISH or G banding karyotyping. chromosomal abnormalities were detected in 15 patients (37%) of which 8 patients (20%) had deletion chromosome 13, 3 patients (7.5%) had complex cytogenetics, 2 patients (5%) had cyclin D1 amplification, 2 patients (5%) with t(11-14) and 2 patients (5%) with t(4-14).

1.6.1 Somatic Rate of NFKB2 rearrangement

We measured the 3' end of NFKB2 of CD38(+) plasma cells and match germ line DNA derived from blood granulocytes of 56 patients included in the study. Our preliminary data showed that that 25 out of 56 had lower NFKB2 3' end mRNA expression levels. To identify whether the loss of NFKB2 3'end resulted from a rearrangement, we performed a NFKB2 break a part FISH in 31 patient of this cohort. Our results demonstrated that 9 (29%) patients with a positive structural defect in this region. In addition, when we expanded the screening with the NFKB2 break a part FISH in 20 MM patients identified outside of our original study, we detected a structural defect in 7/20 patients (35%).

1.6.2 Origin of NFKB2 break point.

To identify potential sites of break and partners rearranged with NFKB2, we performed analysis of the WGS data obtained from Genotypes and Phenotypes (dbGAP) database. We first selected paired end reads in which one read was mapped to NFKB2 and the mate outside of NFKB2. This analysis delineated three potential sites of break clustered in the promoter region, intron 1, and the exon-intron junction of exon 12 (Figure 1A). These results were expanded by performing RNA sequencing in 3 samples from our clinical database (2 non responder and 1 responder patient as control) and found in addition to the break point between exon 12 and 13 another potential site of break near exon 20, both of which had the presence of a repetitive element. To further validate the site of NFKB2 break in our population, we performed long range PCR in 3 cases treated with VD (2 non responders and 1 responder). As shown in figure 2B-C, a break point was located between exons 12 and 14. In addition, these results were confirmed by break a part fluorescent in situ hybridization methods (Figure 2D). Our findings demonstrated that 9 patients out of 31 patients studied had NFKB2 break (29%) and 4 out of 8 patients with low NFKB2 3'end also had NFKB2 breaks.

1.6.3 Somatic NFKB2 rearrangement and response to Bortezomib and dexamethasone treatment

We assessed the influence of the loss of NF-kB 3'end and the presence of NFKB2 rearrangement on the clinical response of patients with multiple myeloma after 4 cycles of treatment with bortezomib and dexamethasone. Figure 2A-B, illustrate the response status and the depth of response with the level of NFKB2 3' end, as displayed by a ratio generated from comparing NFKB2 3' end from CD138 (+) cells and peripheral blood leukocytes. Our univariate analysis demonstrated that patients with low NFKB2 3'end ratio and abnormal FISH experience a lower response rate than those with >1 ratio and a normal break a part FISH (odds ratio [OR] of 10.8;

95% CI 1.99 to 58.16, p<0.01). In addition, history of monoclonal gammopathy of undetermined significance also predicted for a better response to treatment with proteasome inhibitors (OR: 7.6; 95% CI of 1.2 to 47.6, p<0.05). However, after adjusting for potential predictors of patient outcome in our multivariate Cox model analysis we found that only loss of NFKB2 3'end was associated with a significant decrease in bortezomib and dexamethasone response (HR:21.47, 95% CI: 2.99 to 154.399, p <0.01).

We further examined the sensitivity and specificity of the NFKB2 3' end ratio after performing an ROC curve. Using a cut off of 0.83 will allow to predict that patients with a higher value have a 73% chance of achieving an optimal response. In contrast, those with levels lower than 0.83 have a 93.3% chance of not reaching an optimal response. To further evaluate the possible use of NFKB2 break-apart FISH signal as a predictor of response, we performed FISH on whole bone marrow of 31 patients in which QPCR data was available. Using a cut off detected by AUC curve, we identified NFKB2 structural rearrangement in 9 patients (30%) patients of which 6/10 were present in VD-non responders and 3/21 of VD-responders. To validate these findings we performed FISH on CD38+ sorted cell from 23 new patients treated with bortezomib and dexamethasone or carfilzomib, an irreversible inhibitor of the proteasome, and found consistency with our previous results, in which 7 patients demonstrated a NFKB2 positive break signal. Five out of 7 samples of non-responders patients demonstrated a positive break signal while 1/16 were positive in the responders, indicating a chromosome translocation or inversion had disrupted the NFKB2 locus and that this disruption predispose tumors to respond poorly to proteasome inhibitors.

Subsequently, we tested multiple cell lines for NFKB2 rearrangement and identified by target sequencing that HUT88 presents a balance translocation between chromosomes 10 and 3. Taking advantage of this finding we compared the sensitivity of detection between 3'end NFKB2 qPCR 3' end NFKB2 ratio and the break-apart FISH. To this end, we mixed cell line with normal NFKB2, as it is in MM1S, with titrating doses of HUT88. Quantitative PCR was able to detect a minimum of 3% HUT88 cells in the mix, while NFKB2 break-apart FISH was able to detect when the percent of HUT88 reach 10%. The correlation between both tests was r^2:0.98, P<0.02.

The association between pretreatment NFKB2 levels and bortezomib response was further validated in 3 published gene expression and clinically annotated dataset originated from 3 independent clinical trials of MM patients treated with bortezomib. To best distinguish the predictive power of the NFKB2 levels, we compare the affimetrix signal detected by 3 different probes on patients that responded (CR + PR) or progressed to bortezomib treatment from trials 25 and 40. Logistic regression analysis fitting the model outcome response (CR and PR) vs. no

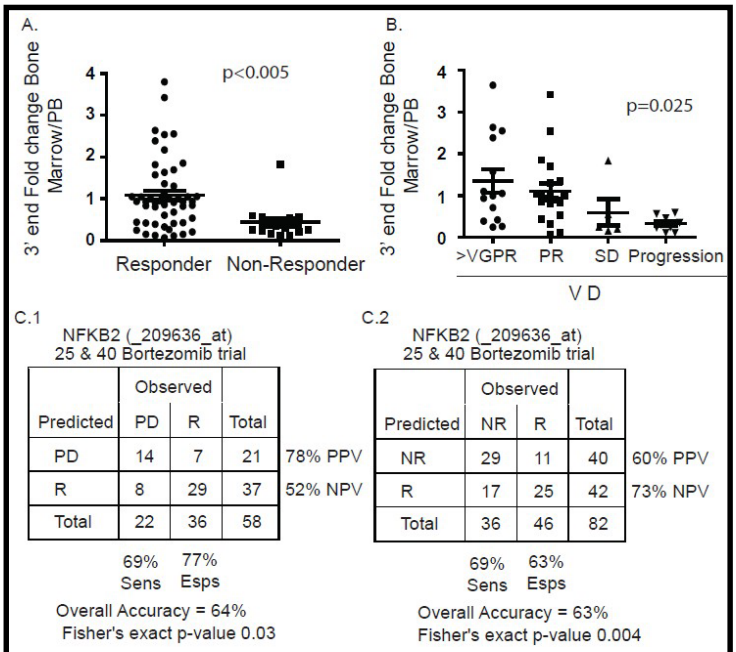


Figure 2. (A) Ratio of NF-kB2 3'end mRNA levels of CD38(+) and peripheral blood granulocytes in bortezomib and dexamethasone responder and nonresponder patients. (B) NF-kB2 3' end ratio according to Bortezomib and dexamethasone response. (C) Binary classification test generate from one of the affymetrix NF-kB2 probes used in patients treated with bortezomib treatment in 2 different clinical trials. Affimetrix units were obtained after RMA normalization of the full dataset.

response (PD) to bortezomib treatment determine that NFKB2 mRNA levels were significantly associated with bortezomib response (probe _207535_s_at : OR: 2.42, 95% CI: 1.12-5.22, OR P-value: 0.025; probe_209636_at: OR: 1.72, 95%CI: 1.16-2.55, OR p-value: 0.007 and probe _211524_at: OR:2.27, 95% CI: 1.17-4.38, OR p-value: 0.015, Figure 2C). We next build a receiver operating curve analysis using bortezomib responders and patients with progression and showed that each probe predicted the response to bortezomib with an overall accuracy that ranged between 64% and 74%(probe _207535_s_at: accuracy 74%, p-value <0.002, probe_209636_at: accuracy 72%, p-value <0.001 and probe _211524_at: accuracy 64%, p-value <0.03). Only probe_209636_at kept its significant overall accuracy when patients that achieve stable disease were included (overall accuracy of 66%, p-value =0.004, Figure 2). This analysis lacked of significance when samples from trial 039 as independent set were used, which could be explained by the notably higher response rates seen in this trial, as well as heterogeneity of the disease.

1.6.4 In vitro data

1.6.4.1Presence of NFKB2 3'end predict bortezomib sensitivity

The capacity to identify that loss of the NFKB2 3'end, by qPCR or FISH analysis, gave us the ability to identify patterns of noncanonical NF-kB pathway dysregulation within MM samples. Since loss of NFKB2 3'end was associated with poor response to bortezomib treatment, we

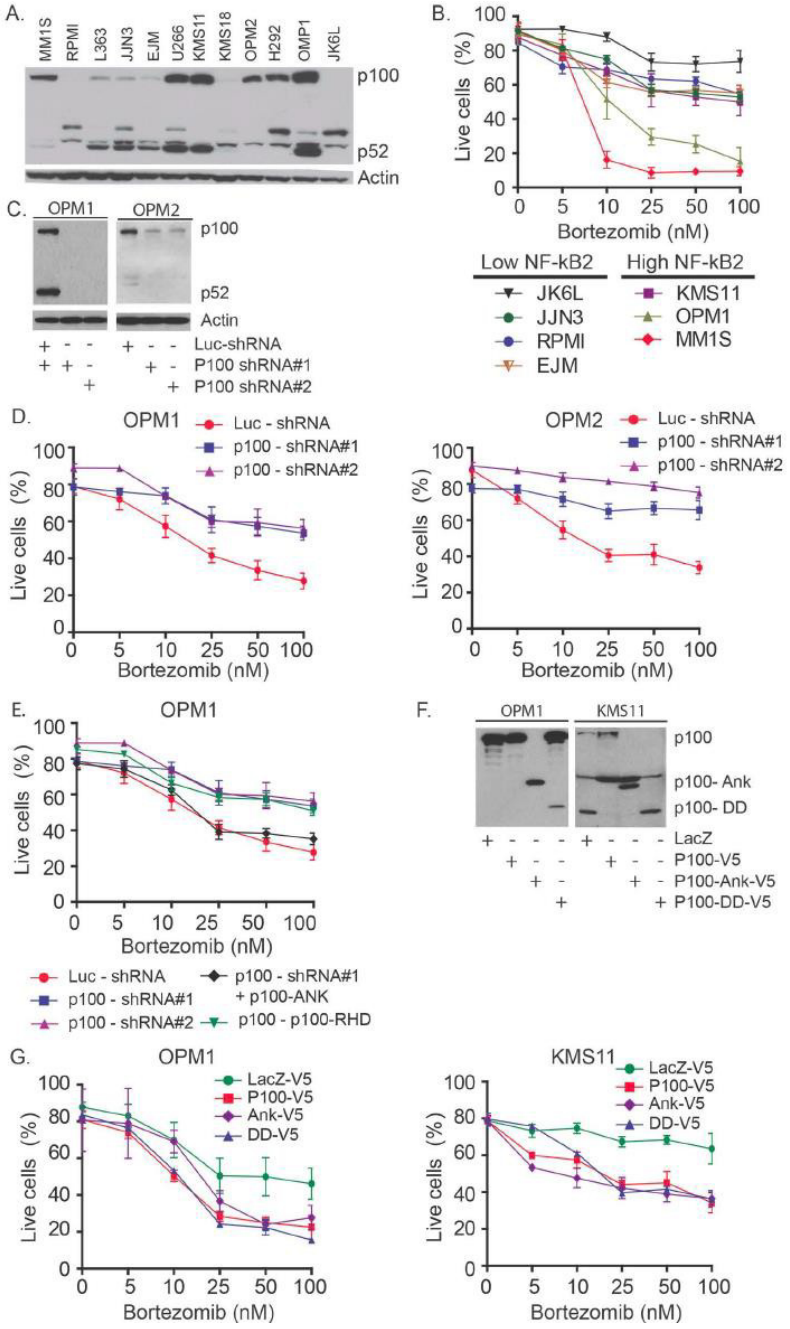


Figure 3. (A) Western Blot analysis of p100(NF-kB2) and p52 in a panel of MM cell lines. (B) Treatment curves of titrating doses of bortezomib. Cells with high or low p100 protein levels were treated for 24 hours. Percent of live cells was measured using an ImageXpress 5000A Automated Acquisition and Analysis System (Molecular Devices), quantitating for Yo-pro-1 or PI -negative cells. (C) Western blot analysis measuring NF-kB2 protein levels in cells stably expressing V5 3' tagged NF-kB2, (D) Reduction of bortezomib sensitivity in NF-kB2 silenced cells. Cell survival measured in a OPM1 and OPM2 cells after stably silencing NF-kB2 expression. (E) Cell survival in NF-kB2 silenced OPM1coexpressing the 3'end (Ankyrin domain, Ank) or the 5'end rel homology domain. (F) Western blot illustrating the expression of the NF-kB2 ankyrin domain, NF-kB2-death domain and LacZ (control) protein. (G) Treatment curves of titrating doses of bortezomib treated cells expressing NF-kB2 or its mutants (DD= death domain).

investigated the role of NFKB2 in bortezomib mediated apoptosis. We screened NFKB2 protein levels in a panel of HMCLs. Among them RPMI, L363, JJN3, EJM, KMS18 and JK6L demonstrated the lowest protein levels of NFKB2 (Figure 3A). These results confirmed previously described alterations in NFKB2 regulatory proteins such as NIK truncations (JJN3, L363 and EJM), NFKB2 frameshift mutation disrupting the C-terminal ankyrin repeat (JK6L) and homozygous deletions of BIRC2/BIRC3 chromosomal locus (KMS18). To determine whether the NFKB2 levels correlated with bortezomib response, we selected cells with low (JJN3, RPMI,

L363, EJM and JK6L) or high (OPM1, MM1S and KMS11) to evaluate cell survival to titrating doses of bortezomib. Cells with low levels of NFKB2 show more resistance to bortezomib treatment than cells with high NFKB2 levels, suggesting that NFKB2 might be important for bortezomib mediated apoptosis (Figure 3B).

1.6.4.2 NFKB2 is important in bortezomib mediated apoptosis.

To determine whether the NFKB2 is involved in bortezomib sensitivity, we silenced NFKB2 in 2 bortezomib sensitive cell lines (OPM1 and OPM2) and tested for their response to bortezomib. Our results demonstrated that silencing of NFKB2 in OPM1 and OPM2 cell lines decrease bortezomib apoptotic effect significantly (Figure 3E-F, $P<0.01$). However, when we restore the expression of the domains contained in the 3' end of NFKB2 (ankyrin domain) in NFKB2 silenced cells, we observed an improvement in bortezomib sensitivity. Furthermore, overexpression of NFKB2 or any of the 3'end domains (Ankyrin or death domain) increased bortezomib apoptotic effect independent of their original sensitivity to bortezomib (Figure 3F-G).

1.6.4.2.1 NFKB2 promotes the complex formation of p62/FADD and caspase-8 to facilitate caspase 8 processing.

Since previous work has established that autophagy and caspase 8 are apical events for mitochondrial activation and cell death during bortezomib treatment, we performed a time course in 2 bortezomib-sensitive cells (MM1S and OPM1) to measure the sequence of events that leads to caspase 3 activation. Caspase 8 was processed to their 43/41 subunits at 2 hours, and to p20 at times correlating with caspase 9 cleavage (6 hours, Figure 4A-B). Supported by these results, we investigated the consequence that silencing NFKB2 has on caspase 8 activation. NFKB2 reduced caspase 8 activation early on followed by 9 and 3 activation (Figure 4B.1 and B.2).

The domains contained in the NFKB2 3'end participate in the formation of a death-inducing signaling complex that links death receptor signals with caspase 8 activation upon irradiation or TNFα treatment. Furthermore, in T cells FADD dependent binding to Atg5-Atg12 in autophagosomes is essential for caspase 8 processing. We therefore investigated whether NFKB2 is linked with several of the autophagy members required for caspase 8 processing during proteasome inhibition. NFKB2-v5 tagged protein was immunoprecipitated after treatment with bortezomib, TNF or control OPM1 cells expressing a 3' end V5 tagged NFKB2 protein. Coprecipitating proteins were analyzed by immunobloting. Significant levels of P62, ATG5-ATG12 conjugate, caspase 8 and FADD were detected as early as 5 minutes in TNF (positive control) or bortezomib treated cells (Figure 4C). Reciprocal co-immunoprecipitation with a

FADD antibody showed that NFKB2, and p62 precipitated with FADD (Figure 4D). Similar results were observed in cells expressing endogenous FADD and NFKB2 protein levels (Figure 4E). To determine, which of these potential NFKB2 binding partners were directly bound to NFKB2, we immunoprecipated FADD in NFKB2 silenced OPM1 cells. Silencing NFKB2 led to a reduction in FADD, P62, caspase 8 binding and increase Atg5/Atg12-FADD binding, suggesting that NFKB2 plays a major role in FADD-P62-Caspase 8 complex formation (Figure 4E). Finally, p62 and caspase 8 colocalization was evaluated in a time course of OPM1 cells treated with bortezomib (10 nM) and demonstrated that p62-caspase 8 complex formation lasted for 6 hours before returning to baseline. Together, these results link NFKB2 with the initiating signaling required for caspase 8 activation during bortezomib treatment (Figure 4F).

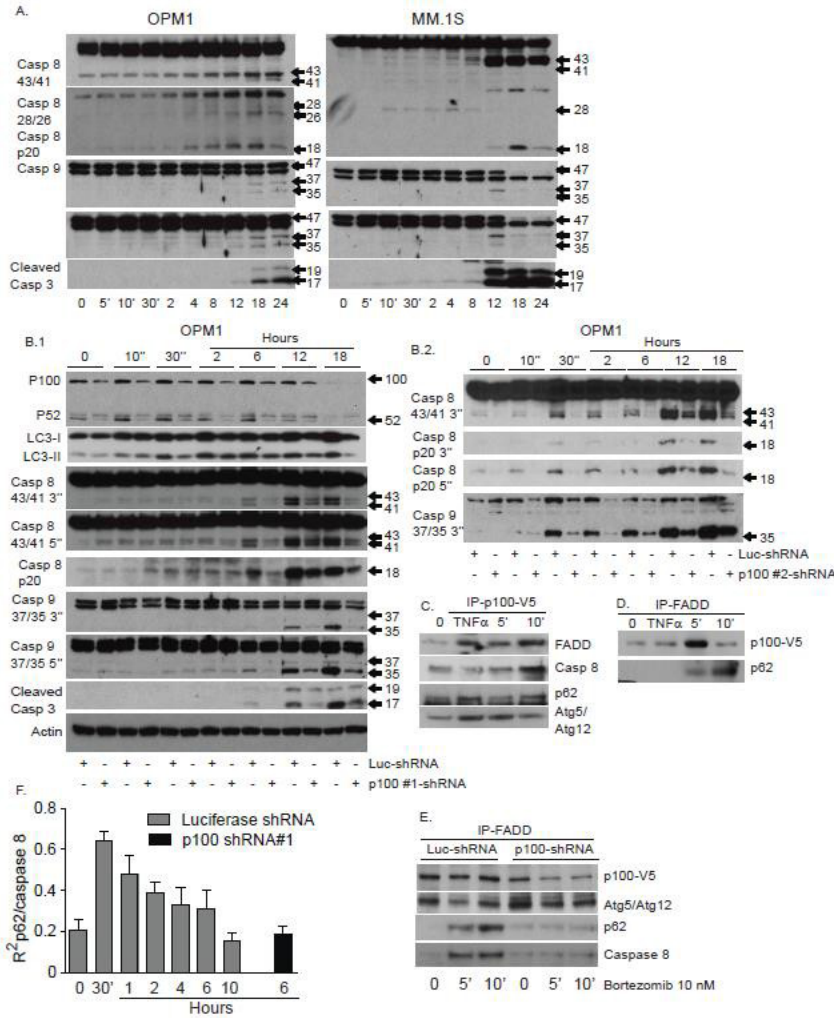


Figure 4. NF-kB2 (p100) is important for bortezomib induction of caspase 8 cleavage. A. Western blot analysis measuring p62, LC3-I and II, or caspase 8, 9 and 3 in OPM1 and MM1S (A) or in OPM1control (Luciferase-shRNA, LUC-shRNA) or NF-kB2 silenced cells (B) during treatment with bortezomib. C-D. Immunoprecipitating FADD or p100-V5 followed by Western blot analysis measuring FADD, caspase 8, p62 and ATG5/12 in OPM1 treated cells with TNFα (10 ng) or bortezomib F. Immunoprecipiation of FADD and western blot analysis of p62, ATG5/12 or caspase 8 was done in control (LUC-shRNA) or NF-kB2 (p100) silenced cells after treatment with bortezomib. F. Immunofluorescence of p62 and caspase 8 in OPM1expressing luciferase- or NF-kB2(p100)- shRNA. Bortezomib=10 nM.

1.7 Study Rationale

Advances in therapeutic combinations have improved the outcome of MM. Although these combination of agents are now improving the outcome, many patients fail in achieving an optimal response and are accompanied with higher toxicities and health care cost. Hence, if we could identify at diagnosis a subset of patients that would benefit from specific therapies, this could lead to higher optimal responses and lower toxicities and healthcare cost. Our proposal answers this need by identifying for the first time whether we can tailor the treatment of relapsed MM patients, as defined below, based on their NFKB2 rearrangement status. To this end, we propose to conduct a prospective; biomarker driven randomized controlled trial to compare the clinical response of relapsed MM patients treated with ixazomib plus dexamethasone versus ixazomib, lenalidomide and dexamethasone based on their diagnostic NFKB2 break apart FISH results. The objectives of the trial are to address whether patients without NFKB2 rearrangements treated with Id can have a similar outcome to those with NFKB2 rearrangements treated with IRd regimen as assessed by their clinical response, monoclonal protein, serum kappa lambda light chains, and bone disease.

Correlative studies in this proposal will characterize the gain of new genetic abnormalities in plasma cells of patients that are refractory or relapsed after Id or IRd treatment. To this end, we will assess for transcribed mutations by performing RNA sequencing (RNA-seq) of plasma cells acquired from bone marrow biopsies obtained pre-randomization and at relapse or in patients with evidence of progression.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of the study is to test whether the NFKB2 rearrangement can guide the selection of treatment (Ixazomib plus dexamethasone (Id) or ixazomib plus lenalidomide and dexamethasone (IRd)) by conducting the 3 following comparisons:

- To compare the response rate at 4 cycles between patients treated with Id and patients treated with IRd and confirm the lack of significant difference in overall response.
- To compare the response rate at 4 cycles between non-rearranged and rearranged NFKB2 treated with Id and confirm that NFKB2 rearrangement is associated with

reduce response rate

- To compare the responses rate at 4 cycles of patients with rearranged NFKB2 treated with Id or IRd and confirm that adding lenalidomide increases the response rate in this population

We assume that adding lenalidomide in the treatment among non-rearranged patients will not further improve the response rate, because our preliminary data suggest that the response rate of non-rearranged patients with Id is expected toreach 95% and has little room to improve. Therefore, the arm non-rearranged NFKB2 gene treated with IRd has been omitted in order to save resources. Our preliminary data has shown that adding lenalidomide to bortezomib, another inhibitor of the proteasome, resulted in response rates of 95% and published data has shown that ixazomib in combination with lenalidomide (len) and dexamethasone (dex) in newly diagnosed multiple myeloma achieved a 92%; hence, has little room for improvement.

2.2 Secondary Objectives

- To determine time to treatment failure (TTF)
- To determine the frequency and severity AE in IRd treated cohort
- To identify novel transcribed mutations associated with Id and IRd resistance in patients with MM.
- To determine the prevalence of NFKB2 rearrangement in Relapsed/Refractory MM patients screened in the study.
- To determine the prevalence of NFKB2 rearrangement according to the type of previous therapies received in all patients screened in the study.
- To determine the toxicity profile of the study drugs according to the presence of NFKB2 rearrangement.
- Delineate transcribed mutations associated with relapse or refractoriness to Id or IRd treatment by RNA-sequencing.

2.3 Hypothesis:

Patients without NFKB2 rearrangement treated with Id will have better outcomes to those with NFKB2 rearranged treated with Id and similar outcome to those NFKB2 rearranged patients treated with IRd.

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- The primary objective of the study is to test whether the NFKB2 rearrangement can guide the selection of treatment (Ixazomib plus dexamethasone (Id) or ixazomib plus lenalidomide and dexamethasone (IRd)) by conducting the 3 following comparisons:
    - To compare the response rate at 4 cycles between patients treated with Id and patients treated with IRd and confirm the lack of significant difference in overall response.
    - To compare the response rate at 4 cycles between non-rearranged and rearranged NFKB2 treated with Id and confirm that NFKB2 rearrangement is associated with reduce response rate
    - To compare the responses rate at 4 cycles of patients with rearranged NFKB2 treated with Id or IRd and confirm that adding lenalidomide increases the response rate in this population

3.2 Secondary Endpoints

- To compare response rates between arms at 8 cycles of treatment
- To determine the frequency and severity AE in IRd treated cohort
- To determine time to treatment failure (TTF)
- To determine the prevalence of NFKB2 rearrangement in Relapsed/Refractory MM patients screened in the study.
- To determine the prevalence of NFKB2 rearrangement according to the type of previous therapies received in all patients screened in the study.
- To determine the toxicity profile of the study drugs according to the presence of NFkB2 rearrangement.
- Delineate transcribed mutations associated with relapse or refractoriness to IDL treatment by RNA-sequencing.

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, 3-arm, phase II clinical trial to study the differential effect in treatment

efficacy in terms of response rate between treatment (Id vs IRd) and NFKB2 mutation status in relapsed patients with multiple myeloma. The potential maximum sample for this study is 90 patients.

At the time of study initiation at a subsite, the coordinating center multi-site coordinator (with additional staff as needed) will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance.

4.2 Treatment Assignment

Eligible patients with relapsed MM will be assigned to each arm according to their NFKB2 rearrangement status. The first 30 patients **without** NFKB2 rearrangement will be enrolled into Arm A and treated with ixazomib and dexamethasone (Id). On the other hand, the first 60 patients **with** NFKB2 rearrangement will be subsequently randomized to receive in Arm B: ixazomib and dexamethasone or in Arm C: Ixazomib, dexamethasone and lenalidomide (IRd) until the specific arm is closed. Randomization is conducted with a block of 2 patients in order to balance the enrollment in each arm (The first of the 2 patients entered consecutively is randomly assigned to one of the 2 arms (Arm B or Arm C) with equal probability and the second one is assigned to the other arm).

Patients will be administered Ixazomib orally at a dose of 4 mg on Days 1, 8, and 15 during a 28-day treatment cycle. Dexamethasone will be administered orally at a dose of 40mg daily on Days 1, 8 ,15 and 22 of a 28 day treatment cycle. In the IRd arm, lenalidomide will be administered orally at a dose of 25 mg daily on Days 1-21 of a 28 day cycle. Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guidelines. Doses of ixazomib, lenalidomide, or dexamethasone may be held or reduced in an attempt to manage toxicity according to the guidelines outlined in Section 6.3.2. Treatment repeats every 28 days for 4 cycles, or beyond, in the absence unacceptable toxicity or if at least a minimal response has been achieved.

Patients will be evaluated at scheduled visits over 3 study periods: Screening, Treatment, and End of Treatment (EOT). The duration of therapy is 4 cycles where patients will be assessed for response after Cycles 1, 2, 3, and 4. Patients may have stem cells mobilized after a minimum of 4 cycles and frozen for future use. Patients deemed appropriate by treating physician for transplant may elect to stop treatment after 4 cycles and proceed to ASCT. At any point during the first 4

cycles of treatment, patients suspected of disease progression (PD) will have response assessments repeated to confirm disease progression (ie, 2 sets of response assessments at least 1 week apart). Patients who do not proceed to ASCT after 4 cycles may remain on trial according to the schedule presented in the Schedule of Events for Cycle 2+ visits. These subjects will continue to be evaluated for disease response at the end of each cycle. Patient without unacceptable toxicity and with at least minimal response should continue treatment until 8 cycles. At the end of Cycle 8 and, per the investigator's discretion, the subject may continue the trial regimen as outlined in the Schedule of Events (Cycle 9+) until withdrawal of consent, disease relapse; unacceptable toxicity or no further clinical benefit is experienced. Toxicity will be evaluated according to the investigators' documentation of AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 and, for neurotoxicity, will be guided by the patients' completion of the Functional Assessment of Cancer Therapy/Gynecology Oncology Group Neurotoxicity (FACT/GOG Ntx) questionnaire (Appendix 16.3). AEs will be assessed, and laboratory values, vital signs, ECGs (at diagnosis) will be obtained to evaluate the safety and tolerability of ixazomib.

Radiological evaluations (skeletal surveys, and as clinically indicated, plain films of symptomatic sites, positron emission tomography-computed tomography [PET-CT], computed axial tomography [CT] scan or magnetic resonance imaging [MRI]) will be employed to assess the status of the patient's multiple myeloma in bone and in extramedullary sites.

Serial blood samples and 24-hour urine collections will be analyzed for M-protein quantification (serum protein electrophoresis [SPEP] and urine protein electrophoresis [UPEP], respectively), serum free light chain assay, immunofixation of serum and urine, and quantification of immunoglobulins. Bone marrow biopsy and aspirate will be obtained before initiation of therapy to evaluate the extent of plasma cell infiltration, NFkB2 rearrangement, cytogenetics and for correlative studies. In addition, bone marrow biopsy and aspirate will be obtained to confirm relapse/refractoriness of the disease and complete remission, as well as for correlative studies (only in relapsed/refractory patients). Disease response will be assessed using modified and updated by the International Myeloma Working Group (IMWG).(Rajkumar 2011, Durie 2006)

4.3 Number of Patients

Approximately 90 patients will be enrolled in this study. Enrollment in this study is defined as the time the patient receives the first dose of ixazomib.

4.4 Duration of Study

The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period may continue until disease progression, unacceptable adverse reaction or other reason for discontinuation. After study treatment discontinuation an end of treatment (EOT) visit will be done at 30 days after the last dose of ixazomib. Patients who discontinue treatment for reasons other than progression of disease will be followed monthly until progression or initiation of subsequent therapy.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and Ixazomib and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide through 90 days after the last dose of study drug. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 90 days after the last dose of study drug. In the event that the male patients choose to agree to practice true abstinence, this must follow the timelines detailed above. All patients assigned to the lenalidomide treatment group must be registered in and must comply with all requirements of the Revlimid REMS™ program.

4. Multiple myeloma diagnosed according to standard criteria either currently or at the time of initial diagnosis.

5. The patient has confirmed relapsed or refractory MM.

6. For patients that relapse following a response to prior treatment with bortezomib or carfilzomib, six months must have elapsed since the last dose of treatment.

7. The patient has received 1 to 3 prior lines of therapy. By definition, a single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of steroids (ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy

8. Patients must have measurable disease defined by at least 1 of the following measurements:

- Serum M-protein ≥1.0 g/dL (≥ 10 g/L) for an IgG myeloma, ≥ 0.1 g/dL for an IgD myeloma or 0.5 g/dL (≥ 5g/L) for an IgA myeloma.

- Urine light chain ≥ 200 mg/24 hours
- Serum free light chain ≥ 10 mg/dL provided the FLC ratio is abnormal.
- Patients with oligo- or non-secretory disease must have bone marrow involvement with at least 30% plasmacytosis on aspiration.

9. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
10. Patients must meet the following clinical laboratory criteria:
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm3 and platelet count ≥ 75,000/mm3. In the case that platelets are between 50,000 -75,000, the patient can be enrolled if the plasma cell count in the bone marrow is superior to ≥50%. To meet this hematological eligibility no transfusion support and hematological growth factor are not allowed within 7 days before study enrollment.
    b. Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).
    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.
    d. Serum creatinine ≤ 2.5 mg/dL or a calculated creatinine clearance ≥ 50 mL/min.

* A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

5.2 Exclusion Criteria

1. The patient is refractory to carfilzomib or bortezomib. (Refractory is defined as patients who never achieved a response and progressed while on carfilzomib or bortezomib or within 60 days of completing treatment).
2. Prior treatment with any investigational proteasome inhibitor within 6 months of study entry.
3. Female patients who are breast feeding or have a positive serum pregnancy test during the screening period.

4. Failure to have fully recovered (ie, > Grade 1 toxicity) from the reversible effects of prior chemotherapy.

5. Diarrhea > Grade 1 according to NCI CTCAE v4.03

6. Prior chemotherapy and/or immunotherapy within 14 days before enrollment. Major surgery within 14 days before enrollment and minor surgery within 7 days prior to Cycle 1 Day 1

7. Radiotherapy within 14 days before enrollment. If the involved field covered ≤ 5% of the bone marrow reserve, the patient may be enrolled irrespective of the end date of radiotherapy.

8. Central nervous system involvement.

9. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

11. Systemic treatment, within 14 days before the first dose of ixazomib, with strongCYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

12. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

13. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially compromise the paient's ability to understand the patient information, to give informed consent, to comply with the treatment according to this protocol or complete the study.

14. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

15. Patient has ≥ Grade 2 peripheral neuropathy or neuropathy with pain, regardless of grade that is seen on clinical examination during the screening period.

16. Known intolerance to IMiDs.

17. History of allergic reaction/hypersensitivity to any of the study medications, their analogues or excipients in the various formulations.

18. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or lenalidomide, including difficulty swallowing.

19. Participation in other clinical trials, including those with other investigational agents not included in this trial, such as monoclonal antibodies, within 30 days of the start of this trial and throughout the duration of this trial.

20. Corticosteroid doses > 10 mg/day of prednisone or equivalent within 14 days prior to Cycle 1 Day 1.

21. Autologous or allogeneic stem cell or bone marrow transplant within 3 months prior to Cycle 1 Day 1.

22. Cytotoxic therapy within 21 days prior to Cycle 1 D1.

23. Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not..

6. STUDY DRUG

6.1 Description of Investigational Agents

6.1.1 Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0, 3.0, and 2.3 mg capsules as stable citrate ester drug substance, ixazomib citrate. The different dose strengths are differentiated by both capsule size and color as described below:

For additional details, please see the ixazomib IB.

6.2 Study Drug Administration

6.2.1 Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 7).

The prescribed administration of ixazomib doses in this study is days 1, 8, 15 of ixazomib in a 28 day cycle.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Every effort should be made to comply with the dose and schedule in cycle unless due to toxicity. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2.2 Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

6.3 Lenalidomide

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory

properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

6.3.1 Lenalidomide Administration

Lenalidomide should be taken once daily at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. Lenalidomide should be swallowed whole with water.

Instruct patients that if they miss a dose of lenalidomide, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take lenalidomide at the usual time. Patients should not take 2 doses to make up for the one that they missed.

Commercial supplies of lenalidomide will be used for this study. Refer to the package insert for full prescribing information

Prescribers must be certified with the REVLIMID REMS™ program by enrolling and complying with the REMS requirements.

Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements.

Pharmacies must be certified with the REVLIMID REMS™ program, must only dispense to patients who are authorized to receive lenalidomide and comply with REMS requirements.

6.4 Dexamethasone

Commercial supplies of dexamethasone will be used in this study. Oral dexamethasone will be given on an outpatient basis. Missed doses of dexamethasone will not be made up.

7. DOSE-MODIFICATION

The patient will be evaluated weekly for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE, version 4.03. Dose modifications may be performed in all cycles of treatment. If toxicities cannot be managed by

dose modification or the patient cannot tolerate the lowest dose of study drug, the patient is to be discontinued from study treatment. Exceptions may be made for patients that are experiencing clinical benefit in discussion with the Lead Principal Investigator.

7.1 Dose Reduction Steps

7.1.1 Ixazomib Dose Reduction Steps

Ixazomib Dose Reduction Steps		
Starting dose	First Dose reduction Step	Second dose reduction Step
4 mg	3 mg	2.3 mg

7.1.2 Lenalidomide Dose Reduction Steps

Lenalidomide Dose Reduction Steps **(Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline).**			
Starting dose	First dose reduction Step	Second dose reduction Step	third dose reduction Step
25 mg	15 mg	10 mg	5 mg

7.1.3 Dexamethasone Dose Reduction Steps

Dexamethasone Dose Reduction Steps		
Starting dose	First Dose reduction Step	Second dose reduction Step
40 mg	20 mg	12 mg

Dexamethasone may be permanently discontinued for toxicity at the discretion of the investigator but the patient can remain on study therapy with lenalidomide and/or ixazomib if tolerated.

7.2 Dose Modification Guidelines during A Cycle Of Therapy

Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of 1 agent and not the other is appropriate (for patients assigned to IRd, if toxicity is related primarily to 1 of the agents. Prior to beginning the next cycle of treatment, refer to the guidelines in Section 7.4. Further clarification can be obtained in consultation with the Principal Investigator. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to guidelines of the most severe toxicity.

7.2.1 Ixazomib and Lenalidomide dose modification Guidelines During a cycle of therapy

A decision regarding which study drug requires dose reduction will be dependent upon the toxicity, its onset, and time course. Alternative dose modifications may be recommended after discussion with the investigator and Principal Investigator to maximize exposure of study treatment while protecting patient safety given that there may be overlapping dose limiting toxicities (eg, thrombocytopenia, neutropenia, rash, and peripheral neuropathy.

Hematologic Toxicity during a cycle of therapy			
Neutropenia			
Absolute Neutrophil Count	**Action on Study Drug (Ixazomib)**	**Action on Lenalidomide**	**Action**
First fall to < 0.5 × 10^9/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; add G-CSF
Return to ≥ 500 × 10^3/mcL within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 0.5 × 10^9/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.10 for myeloid growth factor recommendations
Return to ≥ 500 × 10^3/mcL within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 4 mg, reduce to 3 mg
Third fall to < 0.5 × 10^9/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.10 for myeloid growth factor recommendations
Return to ≥ 500 × 10^3/mcL within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg

Fourth fall to < 0.5 × 10^9/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to ≥ 500 × 10^3/mcL within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg.
Fifth fall to < 0.5 × 10^9/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.10 for myeloid growth factor recommendations.
Return to ≥ 500 × 10^3/mcL within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg
Thrombocytopenia			
Platelet Count	**Action on Study Drug (ixazomib)**	**Action on Lenalidomide**	**Action**
First fall to < 30.000/mm^3	Interrupt treatment	Interrupt treatment	Follow complete blood counts (CBC) weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 4 mg, reduce to 3 mg
Third fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg
In some severe situations, both lenalidomide and study drug may be interrupted if needed, or alternative dose modification management implemented based on discussion between the treating physician and Principal Investigator Angioedema and Grade 4 rash have been reported with lenalidomide and should result in lenalidomide discontinuation.			

Non-Hematologic toxicity during a cycle of therapy		
CTCAE Category	**AGENTS**	**Toxicity During a Cycle**
Non-blistering rash Grade 4	**Lenalidomide/ Ixazomib**	Discontinue lenalidomide and ixazomib. Withdraw participant from the study. Patient should be treated immediately following institutional guidelines.
Desquamating (blistering) rash-any Grade or Erythema multiforme ≥ Grade 3	**Lenalidomide/ Ixazomib**	Discontinue treatment. Withdraw participant from study. Patient should be treated immediately following institutional guidelines.
New onset of Hyperthyroidism or Hypothyroidism	**Lenalidomide**	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide at investigator's discretion.
Neuropathy Grade 2 peripheral neuropathy with pain or ≥Grade 3 Grade 4	**Lenalidomide Ixazomib**	Hold ixazomib. Follow weekly. If the toxicity resolves to ≤ grade 1(or baseline), restart ixazomib at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of ixazomib one dose level at the start of the next cycle. Omitted doses are not made up. For recurrent Grade 2 peripheral neuropathy with pain or grade 3 neuropathy, hold treatment. If the toxicity resolves to ≤ grade 1(or baseline), reduce lenalidomide and /or ixazomib at investigators discretion. (IRd treatment group) Discontinue treatment. Withdraw participant from study.
Herpes Zoster reactivation any grade	**Lenalidomide Ixazomib**	Hold ixazomib and lenalidomide (IRd treatment group) until lesions are dry. Initiate antiviral therapy. (maintain dose level)
Venous Thrombosis/embolism ≥ Grade 3	**Lenalidomide/ Ixazomib**	Hold therapy and start full anticoagulation as appropriate; restart at investigator's discretion (maintain dose level).

Other Lenalidomide or Ixazomib related non-hematologic toxicity Grade ≥ 3	**Lenalidomide Ixazomib**	Determine attribution (IRd treatment group) of toxicity and hold appropriate therapy. Follow at least weekly. If toxicity resolves to ≤ grade 1 or baseline, resume therapy with one level dose reduction.
Grade 4 related non-hematologic toxicity		Consider permanent discontinuation of therapy. Exceptions may be made following discussion with the Lead Principal Investigator for patients that are experiencing clinical benefit.

7.3 Dexamethasone dose modification Guidelines

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema >Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness	Decrease dexamethasone dose by one dose level. If weakness persists

	> Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

Dexamethasone may be permanently discontinued for toxicity at the discretion of the investigator but the patient can remain on study therapy with Lenalidomide and/or ixazomib if tolerated.

7.4 Criteria for Initiation of A New Cycle of Therapy

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3. For patients with to >50% plasma cells at baseline and platelets count between 50 – 75,000/mm^3, treatment should be adjusted according to the dose modification guidelines described in section 7.2.1
- All other non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate weekly. Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery or newly encountered toxicity reduce the dose of the drug contributing to the toxicity by one dose level at the start of the next cycle. Only one dose level reduction of one or both drugs should be made per cycle. The maximum delay before treatment should be discontinued will be 4 weeks (including if there is required stem cell harvesting where a 4 week delay is also acceptable). Patients in whom there may be clinical benefit, in the absence of disease progression, as per their treating physician, treatment may be continued after discussion with the Lead Principal Investigator and Millennium Pharmaceuticals, Inc./Takeda

7.5 Concomitant Medications

All concomitant medications administered from the time of informed consent signature through 30 days after the end of treatment (last dose or investigator/patient decision to discontinue, whichever is later) are to be reported on the appropriate CRF for each patient.

7.5.1 Excluded Concomitant Medications and Procedures

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: If there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 14 days prior to study drug dosing for any dosing day

7.6 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT_3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.

- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Treatment doses of antiviral therapy such as acyclovir may be administered if medically appropriate.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

7.7 Required/Recommended Concomitant Therapy

- **Prophylaxis against Risk of Infection:** Antiviral therapy such as acyclovir or valacyclovir should be initiated at the onset of administration of ixazomib. Other antivirals are also acceptable.

- **Prophylaxis against Risk of Deep Vein Thrombosis:** Lenalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors, unless there is an excess risk of bleeding. Aspirin 81 mg daily is required to be initiated at the onset of administration of lenalidomide unless contraindicated or alternate anti-coagulation (e.g. LMWH) is used for patient at high risk.

- **Prophylaxis against pathologic fractures:** Bisphosphonates such as zoledronic acid should be initiated at the onset of administration of ixazomib.

7.8 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

- When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin Cmax was increased by 14%. Periodic monitoring of digoxin plasma levels in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication is recommended during administration of lenalidomide.

7.9 Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Lenalidomide can cause fetal harm when administered during pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Females of child bearing potential* and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

*A female of child bearing potential is any sexually mature female who:

1) has not undergone a hysterectomy or bilateral oophorectomy; or

2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

7.9.1 Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide or 90 days following discontinuation of ixazomib. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide and ixazomib. ARM A and B: FCBP on this arm will not be taking lenalidomide. Females of reproductive potential in these arms must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to the first dose of ixazomib. A pregnancy test will be formed at day one on all future cycles. ARM C: This arm will be taking lenalidomide. Females of reproductive potential must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide and ixazomib. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of lenalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of lenalidomide. All study participants on Arm C must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program.

7.9.2 Males

Lenalidomide is present in the semen of males who take lenalidomide. The effects of ixazomib are unknown. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide or ixazomib and for up to 28 days after discontinuing lenalidomide or 90 days after discontinuation of ixazomib, even if they have undergone a successful vasectomy. Male patients taking lenalidomide or ixazomib must not donate sperm. In the event that the male patients choose to agree to practice true abstinence, this must follow timelines detailed above. All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program.

7.10 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib and lenalidomide treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB and in the package insert for lenalidomide.

7.10.1 Thromboembolism Prophylaxis

Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors, unless there is an excess risk of bleeding. For patients at high risk, thromboprophylaxis

according to ASCO guidelines or institutional standard of care is recommended.

7.10.2 Prophylaxis against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.

7.10.3 Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

7.10.4 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

7.10.5 Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity such as lenalidomide. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

The lenalidomide induced rash is characterized as generalized, maculopapular, morbilliform, urticarial, papular, often with pruritus. Per the package insert, discontinuation should be considered for Grade 2-3 skin rash and discontinuation definitely for Grade 4 rash. However,

serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Erythema Multiforme have been reported. Lenalidomide interruption or discontinuation should be considered as described in the Package Insert/Summary of Product Characteristics. (lenalidomide product label)

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

7.10.6 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib and/or lenalidomide (IRd treatment group) administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

7.10.7 Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib and/or lenalidomide (IRd treatment group) administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 7.2.1).

7.10.8 Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

7.10.9 Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

7.10.10 Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

7.10.11 Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

7.11 Preparation, Reconstitution, and Dispensing

ixazomib and lenalidomide are anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib and lenalidomide capsules.

7.12 Packaging and Labeling

7.12.1 Ixazomib

The study drug ixazomib capsules will be provided by Millennium/Takeda. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. The drug product is provided in strengths of 4.0, 3.0 and 2.3 mg capsules.

7.12.2 Lenalidomide

Lenalidomide is commercially available and will be labeled for commercial use.

7.12.3 Dexamethasone

Dexamethasone is commercially available and will be labeled for commercial use

7.13 Storage, Handling, and Accountability

7.13.1 Ixazomib

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F or 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium/Takeda. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F or 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

The study pharmacist or designee at the site will be responsible for handling, dispensing study drug, completing associated documentary paperwork, handling dispensing log/accountability form. Each time study medication is dispensed for a patient, the following information be recorded: the patient's initials, the patient's study number, tablet strength, the number of tablets dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study. The Investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

7.13.2 Lenalidomide

Care should be exercised by caretakers handling lenalidomide. Lenalidomide capsules should not be opened or crushed. If powder from lenalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If lenalidomide contacts the mucous membranes, flush thoroughly with water.

7.13.2.1 Storage

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Only enough lenalidomide capsules for 1 cycle of therapy may be provided to the patient each cycle.

7.14 Disposition of used supplies

All used bottles or packs of study drug must be destroyed in an appropriate manner according to the standard practice. Destruction of such supplies will be documented. During the trial and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be redispensed. No other utilization of MLNN9708 or lenalidomide intended for use in this study will be authorized. The

Principal Investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drugs.

7.15 Other Safety Issues

7.15.1 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of a product that is considered BOTH excessive AND medically important. All occurrences of overdose must be reported as an SAE. Monitor adverse events as instructed in the schedule of events and as clinically indicated.

8. STUDY CONDUCT

8.1 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB).

8.2 Enrollment

Enrollment in this study is defined as the time the patient receives the first dose of any study drug. Procedures for completion of the enrollment information are described in the Study Manual.

8.3 Treatment Group Assignments

Patients will be segregated according to the results of the NFKB2 break apart FISH test. For those patients without splits in NFKB2 will be assigned to ixazomib and dexamethasone. Patients with evidence of a split in NFKB2 will be randomized to ixazomib and dexamethasone or ixazomib, lenalidomide and dexamethasone as described in Section 4.1

9. STUDY PROCEDURES

Patients will be evaluated at scheduled visits over 3 study periods: Screening, Treatment and End of Treatment (EOT).

Refer to the Schedules of Events for timing of all assessments:

Additional details are provided as necessary in the sections that follow.

9.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

For participating institutions, after each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail.

9.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria (see Section 5.0) will be assessed during screening (up to 21 days before the first dose of study drug).

For multi-site institutions, The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-5071) within 14 days after pre-registration but no later than 2 business days prior to the scheduled treatment visit. Eligibility will be confirmed by the site investigator or co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria.

9.3 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.4 Medical History and Physical Examination

A complete medical history is to be obtained at screening including diagnosis and staging of multiple myeloma. The history should include a review of all current medications as well as any prior radiation therapy and antineoplastic therapy.

A complete physical examination, including a neurologic examination, is to be conducted at the Screening visit and at the EOT visit.

A symptom-directed physical examination, including a neurologic examination, is to be conducted at the on Day 1 of each treatment.

9.5 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale at the following visits: Screening; Day 1 of each treatment cycle; and the EOT visit. [29]

9.6 Vital Signs, Body Weight and Height

Measurement of vital signs, including oral temperature, blood pressure, and heart rate will be obtained during the following visits: Screening on Day 1 of each treatment cycle, blood pressure and heart rate measurements will be taken and EOT.

Body weight (kg) will be determined at the Screening visit, on Day 1 of each treatment cycle, and at the EOT visit. Height (cm) will be measured at the Screening visit only.

9.7 Pregnancy Test

ARMs A and B: FCBP on this arm will not be taking lenalidomide. Females of reproductive potential in these arms must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to the first dose of ixazomib. A pregnancy test will be performed at day one on all future cycles or every 14 days if she has irregular menstruation.

ARM C: This arm will be taking lenalidomide. FCBP must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide and ixazomib. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of lenalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of lenalidomide.
* FCBP - A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

9.8 Clinical Laboratory Evaluations

The M-protein quantification (SPEP and UPEP), the serum free light chain assay, immunofixation of serum and urine, quantification of Ig, and all safety laboratory assays are to be performed locally.

9.8.1 Hematology

Hematology will be analyzed locally and includes the following:

- Hemoglobin
- Hematocrit
- Platelet Count
- WBC Count with Differential

A blood sample for hematology testing will be obtained at screening (within 21 days of the first dose of study drug), prior to dosing on day one of each cycle, day 15 of cycle 1, and more

frequently if clinically indicated and at the EOT visit.

9.8.2 Serum Chemistry

Serum chemistry samples will be analyzed locally and includes the following:

- Blood urea nitrogen (BUN)
- Albumin
- Calcium
- Creatinine
- Total Bilirubin
- Uric Acid
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- Glucose
- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Phosphorus

A blood sample for clinical chemistry testing will be obtained at screening (within 21 days of the first dose of study drug), on Days 1 of each treatment cycle, on day 15 of cycle 1, and at the EOT visit.

9.8.3 β2-Microglobulin

A blood sample will be collected at screening for serum β2-microglobulin testing; results will be analyzed locally.

9.8.4 Serum Kappa/ Lambda measurement

A blood sample will be collected at screening and before each cycle for serum Serum Kappa/ Lambda free light chain measurement; results will be analyzed locally.

9.8.5 Urinalysis

A urine sample for microscopic urinalysis will be collected at screening.

9.9 Computed Tomography/Magnetic Resonance Imaging

For patients with documented extramedullary disease, a PET-CT scan, CT scan, or MRI scan will be performed at screening (within 4 weeks of the first dose of study drug) for evaluation of disease. If disease is documented at screening, a repeat PET-CT scan, CT scan, or MRI scan should be performed as required to document response or progression at the EOT visit.

All follow-up scans should use the same imaging modality used at screening.

9.10 Skeletal Survey

A complete skeletal survey, using roentgenography, will be performed at screening (within 4 weeks of the first dose of study drug). If a patient has lytic lesions at screening, then a skeletal survey, PET/CT, or plain film of symptomatic sites must be repeated at the End of Treatment visit. In addition, if there are symptoms or signs that suggest increased or new bone lesions, the skeletal survey or plain film of symptomatic sites may be repeated any time during the study and at the EOT visit. A PET-CT may be done at screening in place of a skeletal survey provided that the same modality for assessment is used throughout the study. Other assessments and scans for extramedullary disease, such as a CT or MRI scan, may be required to better characterize some lesions, especially at screening, to delineate the sites and measurements of extramedullary disease.

Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.11 Quantification of M-Protein

A blood and twenty-four (24)-hour urine sample will be obtained at screening, on Day 1 of Cycle 1, every treatment cycle (beginning at Cycle 2, Day 1) no later than the first dosing day, and at the EOT visit. Thereafter it is left at the discretion of the local physician.

9.12 Serum Free Light Chain Assay

A blood sample will be obtained at screening, on Day 1 of Cycle 1, every treatment cycle (beginning at Cycle 2, Day 1) no later than the first dosing day, and at the EOT visit for the serum free light chain assay. Blood samples will be measured locally.

9.13 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at screening, on Day 1 of Cycle 1, every treatment cycle (beginning at Cycle 2, Day 1) no later than the first dosing day, and at the EOT visit.

9.14 Bone Marrow Biopsy/Aspiration

9.14.1 Morphology

Bone marrow biopsy/aspiration (aspiration required biopsy optional) samples will be obtained at screening (up to 4 weeks before the first dose of study drug) for evaluation of disease. Bone marrow biopsy is to be repeated to assess suspected CR if applicable and at the EOT. This sample will be evaluated locally. In addition, Empire genomics is receiving the baseline bone marrow aspirate to do clinical grade FISH to check for NFKB rearrangements so patients can be assigned to the different treatment groups. The remainder of the baseline sample will be shipped backed to Emory and stored for future genomic analysis which will include RNA sequencing. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

9.14.2 Cytogenetics

A bone marrow aspirate sample will be obtained at screening (up to 4 weeks before the first dose of study drug) for evaluation of cytogenetics. This evaluation will be performed locally.

9.14.3 Biomarkers

Bone marrow for the determination of NFKB2 split signal and RNA sequencing will be obtained from screening bone marrows prior appointment to a treatment arm. The first is being performed on the baseline sample which will be sent to Empire Genomics to have clinical grade FISH analysis to look at the NFKB2 split and be able to assign patients to specific arms. In addition, bone marrow samples will be obtained, at relapse or in refractory patients to evaluate for be transcribed mutations associated with poor response to ixazomib and dexamethasone or ixazomib, lenalidomide and dexamethasone. These samples will be shipped Emory to be purified and stored for RNA sequencing analysis to look for additional biomarkers

9.15 Quantification of Immunoglobulins

A blood sample for quantification of immunoglobulins (IgM, IgG, and IgA) will be obtained at screening, on predose Day 1 of Cycle 1, every treatment cycle (beginning at Cycle 2, Day 1) no later than the first dosing day, and at the EOT visit.

9.15.1 Blood Sample for Genotyping- Germline DNA and RNA

One 5-mL blood sample will be collected during screening or on Cycle 1, Day 1 before the first dose of Id or IRd is administered to assess potential biomarkers that predict response to Id vs IRd. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

9.16 Pretreatment Events and Adverse Events

Monitoring of AEs will be conducted throughout the study. AEs will be reported from the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy. Serious pretreatment events will be reported from the time of the signing of the ICF up to first dose of study drug. SAEs will be reported from the first dose of study drug up through 30 days after administration of the last dose of study drug or until the start of subsequent antineoplastic therapy. All SAEs will be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

9.17 Stem Cell Collection and Autologous Stem Cell Transplantation

Patients who are eligible for and elect to undergo ASCT may undergo stem cell mobilization and autologous peripheral blood stem cell (PBSC) collection at any time after the fourth treatment cycle and ASCT at any time after the fourth treatment cycle. Stem cell mobilization and collection will be performed according to the institutional guidelines at the respective investigative sites.

Patients may delay the start of a treatment cycle for a maximum of 4 weeks for stem cell mobilization and collection. Patients may elect to stop treatment after 4 cycles and proceed to ASCT at the discretion of the treating physician and participating institution. Patients going on to ASCT must complete all EOT visit procedures prior to undergoing ASCT. Patients who undergo ASCT(s) will provide blood and urine samples every 16 weeks following the ASCT(s) for the assessments of SPEP, UPEP, immunofixation of serum and urine, and serum free light chains until the occurrence of PD. If PD is determined, the date of progression should be recorded and the patient should enter long-term follow-up for survival and alternate therapy.

9.18 Premedications and Concomitant Medications and Procedures

Premedications and concomitant medications and therapy will be recorded from the time that the informed consent form (ICF) is signed through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy. See Section 7.5 for a list of prohibited and allowed concomitant medications and therapies.

10. STATISTICAL AND QUANTITATIVE ANALYSES

10.1 Statistical Methods

10.1.1 Study design and Power Consideration

This is an open-label, 3-arm, phase II clinical trial to study the differential effect in the treatment efficacy in term of response rate between treatment (Id vs IRd) and NFKB2 rearrangement status in relapsed patients with multiple myeloma. The potential maximum sample for this study is 90 patients. This novel design is a hybrid of two biomarker designs, i.e. the target/enrichment and stratified/interaction design that was necessary to address comparisons based on experimental regimens and the focus on non-responsive (absence of rearrangement) patients. Eligible patients will be first screened by their NFKB2 rearrangement status. The first 30 patients without NFKB2

rearrangement will be enrolled into Arm A and treated with Id. The first 60 patients with NFKB2 rearrangement will be randomly assigned to Arm B and be treated with Id or to Arm C and be treated with IRd until the specific arm is closed. Randomization is conducted with a block of 2 patients in order to balance the enrollment in each arm (The first of the 2 patients entered consecutively is randomly assigned to one of the 2 arms (Arm B or Arm C) with equal probability and the second one is assigned to the other arm).

Within arms: Before the study is completed, the response rate of each arm is monitored separately and compared to the historical RR of 30%. The Arm B is used as reference in the study, so that no interim analysis is proposed for the arm and a total of 30 patients without rearragement will be recruited without stopping. The sample size of 30 in Arm B will achieve a power of at least 80% at the significance level of 0.05 to claim that Arm B has equivalent RR as the historical RR of 30% assuming an equivalence tolerance of +/- 20% when the true RR of Arm B is approximately 30%.

Arm A or Arm C is designed to detect an improved RR of 60% vs. 30% using Simon's 2-stage Optimum design with a power of at least 90% and an alpha error of 5%., respectively. Ten (10) evaluable patients will be enrolled into stage I. An interim analysis will be conducted after the stage I. If 3 or less patients in the arm demonstrate objective response, then the arm is closed and concluded with no potential better RR than the historical control RR of 30%. At least 4 objective responses are required to proceed to stage II accrual of 20 additional patients for a total of 30 patients per arm. After the arm is closed with a maximum sample size of 30 patients, if 13 or less patients with objective response, the arm is deemed as no potential better RR than the historical RR of 30%. At least 14 patients must achieve objective response for the particular treatment arm A or C to claim that their response rates are significantly better than the historical RR of 30%. Arm A or Arm C has 65% probability of stopping early and 5% probability of declaring the treatment effective if the true proportion is 30%. The probability of declaring the treatment effective is at least 90% if the true RR is 60%.

Table 8. Power and Sample Size for Testing the Equivalence between RR of Arm B and Historical RR.

Equivalence is defined as within +/- 20% around the historical RR as of 30%: P0 = 30% & D = +/-20% Power = 80%; α = 0.15	
Maximum Sample Size	30
Lower Limit for Response Rate Rejecting Equivalence Upper Limit for Response Rate Rejecting Equivalence	10% 50%

Table 9. Power and Sample Size for Arm A and C, Respectively.

Primary Efficacy Decision Using Simon's Optimum Design Based on RR: P0 = 30% vs. P1 = 60% Power = 90%; α = 0.05	
First Stage Sample Size Upper Limit for First Stage Rejection of Drug	10 3
Maximum Sample Size Upper Limit for Second Stage Rejection of Drug	30 13

Between Arms: Any treatment arm closed to accrual after the first stage interim analysis will be considered an inferior arm and will be excluded from final pairwise comparison. After the study completes, Arm A and C are compared to Arm B using one sided t-test for the superiority in the response rate, respectively. Assuming the expected RR for Arm A or C is about 60% and the expected RR for Arm B is 30%, the sample size of 30 patients per arm will achieve a power of 80% at the significance level of 0.15 to detect the improvement in RR for Arm A or C from 30%

to 60%.

Arm A is compared to Arm C for the equivalence in response rate assuming the equivalence tolerance in response rate is within +/-30% and their true response rates are around 60%. With two sided t-test, the sample size of 30 patients per arm will achieve a power of at least 75% at the significance level of 0.05 to claim that the Arm A and C have equivalent RR when their true RRs are 60%.

Table 10. Power and Sample Size for Arm A or Arm C Compared to Arm B, Respectively.

Superior Response Rate for Arm A, or C than Arm B: P0 = 30% vs. P1 = 60% (P1 > P0) Power = 80%; α = 0.15	
Sample Size of Arm B	30
Sample Size of Arm A or C	30

Table 11. Power and Sample Size for Testing the Equivalence in Response Rates between Arm A and Arm C.

Equivalence is defined as within +/- 30% around the expected RR as of 60%: P0 = 60% & D = +/-30% Power = 76%; α = 0.05	
Sample Size of Arm A	30
Sample Size of Arm C	30

10.1.2 Populations for Analysis

Evaluable for Toxicity: Patients will be considered evaluable for toxicity if they receive any study drug. Patients will not be replaced based on toxicity.

Evaluable for Response: Patients will be considered evaluable for response if they have baseline disease assessments, received at least one cycle of therapy and have had their disease re-evaluated.

These patients will have their response classified according to the IMWG response criteria. All patients who are not evaluable for response may be replaced.

Evaluable for RNA sequencing analysis:

- Receive a bone marrow prior starting protocol-specified dosing regimen;
- Receive the protocol-specified dosing regimen during Cycle 1 without dose reductions or interruptions;
- Do not receive any excluded concomitant medications through the completion of the treatment;
- Evidence of progression or stable disease of protocol-specified regimen; and
- Have sufficient bone marrow and peripheral blood sample for RNA extraction and sequencing analysis.

10.1.3 Response Assessment

Response assessments will be performed no later than the first day of every treatment cycle beginning with Cycle 2, Day 1. Response and relapse categories are as follows:

- Complete response CR
- *Subcategory: stringent complete response* *sCR*
- Partial response PR
- *Subcategory: very good partial response* *VGPR*
- Stable disease SD
- Minimal response MR
- Progressive disease PD

CR should be confirmed with follow-up assessments of serum protein electrophoresis (SPEP), UPEP, immunofixation of blood and urine, and serum free light chains. One bone marrow assessment has to occur to document CR; no second bone marrow confirmation is needed. PD may be confirmed per IMWG criteria. Please note that in order to determine a response of sCR, bone marrow immunohistochemistry or immunofluorescence for kappa:lambda ratio, as well as serum free light chain assay, should be performed for all patients suspected to be in CR to meet

this response category's requirements. Please see section 15.3 for further details.

10.1.4 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median [range]) will be provided. For categorical variables, patient counts and percentages will be provided. Status of NFKB2 rearrangement at baseline will be listed.

Response rates and depth of response will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR, and exact 95% confidence intervals will be calculated for these estimates. Response defined as per modified IMWG criteria. Time to response, duration of response, and survival will be estimated using the product-limit method of Kaplan and Meier. The rate of MR will also be evaluated to determine the clinical benefit response.

10.1.5 Efficacy Analysis

The response criteria used in this study is the updated version of the IMWG (See Section 15.3). [30] The efficacy analysis will mainly focus on the response rate at 4 cycles. Other efficacy parameters, including but not limited to time to response and DOR, will be presented in listings and summarized if appropriate.

10.1.5.1 Primary Efficacy

The primary endpoint is a response rate of VGPR or better after 4 cycles.

The primary efficacy analysis will be based on the Response-Evaluable population. Estimates of the CR + VGPR rates will be presented with 2-sided 95% exact binomial confidence intervals.

10.1.5.2 Secondary Efficacy

The secondary efficacy parameters include the overall response rate (CR + VGPR + PR), PR, stable disease (SD) or progression rate at cycle 4 and CR, sCR, VGPR, combined CR + VGPR rate, and PR at cycle 8 (if patient continues on treatment), and time to response, DOR, TTP and PFS.

Time to response is defined as the time from the date of first dose of study treatment to the date of the first documentation of a confirmed response in a patient who responded.

The DOR is defined as the time from the date of first documentation of a confirmed response to the date of first documented PD.

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of PD.

PFS is defined as the time from the date of first dose of study treatment to the date of first documented PD or death.

The response rates, time to response, and DOR will be analyzed based on the Response-Evaluable population. Time to response may also be measured in the population of patients with a confirmed response. The response rates will be analyzed similarly to the primary endpoint. Time to response, DOR will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates.

10.1.5.3 ORR in the Subset of High-Risk Patients

ORR will be presented with 2-sided 95% exact binomial confidence interval in the subset of high-risk patients determined by cytogenetics.

10.1.5.4 Autologous Stem Cell Transplant Evaluation

For patients who elect to proceed to stem cell harvesting and ASCT, summary tables will be presented for the number of CD34+ cells (per kg) collected, as well as engraftment parameters if available.

10.1.6. Exploratory Biomarker Analysis

Gene expression and - RNA sequencing (RNA-seq). To assess for gene expression and transcribed mutations associated with poor response to Id or IRd, we will extract RNA from plasma cells and its corresponding normal counterpart using a Quiagen RNAeasy Kit. RNA quality will be accessed using the Agilent RNA 6000 Nano kits with the Agilent 2100 Bioanalyzer. RNA-Seq library preparation will be performed using a minimum of 100 ng of high quality (RIN≥ 8.0). NGS from RNA will be performed in our Cancer Genomics Shared Resource (CLIA#11D1086150). The RNA-Seq sample library preparation will be performed using the Illumina TruSeq kit with assisted automation using Beckman Coulter's SPRIworks HT system. All isolates will be individually barcoded, and RNA-Seq data will be generated using 100x100 paired end reads for each sample using an Illumina HISeq2000 instrument.

Gene expression. All sequencing reads will be evaluated for quality using FastQC software. Depending on the quality control metrics of the data, the reads might be trimmed using SeqTK software. Following trimming, pair end reads will be aligned to reference human genome (GRCh37/hg19) using BWA software. Expression counts per gene will be obtained using Cufflinks software by counting the number of reads or read pairs (also known as fragments) aligning concordantly within a pair and uniquely to a given gene. Differential gene expression will be computed by pairwise *t*-tests on the variance-stabilized counts followed by correction for multiple testing using the Benjamini–Hochberg method.

Identify transcribed mutations. To determine the sequence of mutations associated with poor response to Id or IRd, we will compare the mutational analysis of all samples against the results obtained from time 0. To this end, we will first align paired-end reads using BWA pipeline and detect splices representing translocations, inversions and other distant fusions within a single read end using TopHat software. These distant splices provided one set of candidate fusions for the subsequent testing stage. The other set of candidate fusions derived from: 1) unpaired unique alignments, in which each end of the paired-end read aligned uniquely to a different chromosome, and 2) paired reads, in which each end aligned uniquely to the same chromosome, but with an apparent genomic distance that exceeded 200,000 bp or with genomic orientations that suggested an inversion or scrambling event. Candidate fusions will then filtered against known transcripts from RefSeq. We will require that both fragments flanking a distant splice, or both ends of an unpaired or discordant paired-end alignment, map to known exon regions. This filtering step eliminated approximately 90% of the candidates. For the goal of this project we will further eliminate apparent read-through fusion events involving adjacent genes in the genome, which are thought to be transcriptional rather than a genomic origin.

For the remaining candidate fusion events, we will construct artificial exon–exon junctions consisting of the exons distal to the supported donor exon and the exons proximal to the supported acceptor exon. The exons included in the proximal and distal computations will be limited so that the cumulative length along each gene was within an estimated maximum insert length of 200 bp. As a control, we will also construct all exon–exon junctions consisting of combinations of exons within the same gene, for all genes contributing to a candidate fusion event. We will extract reads that aligned to an intergenic junction corresponding to a candidate fusion, but not to a control intragenic junction.

To filter the results of the re-alignment, we require that each candidate fusion have at least one read with an overhang of 20 bp. We also require that each candidate fusion have at least 5 supporting reads. For each remaining candidate fusion, we will align the two component genes

against each other using BWA and eliminate the fusion if the alignment had any region containing 60 matches in a window of 75 bp. We will also align the exon–exon junction against each of the component genes and eliminate the fusion if the alignment had coverage greater than 90% of the junction and identity greater than 95%.

10.1.7 Safety Analysis

Toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of Id or IRd combinations.

Safety will also be evaluated by the incidence of treatment-emergent AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the Safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent events will be tabulated. *Treatment-emergent* is defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study medication or until the start of subsequent antineoplastic therapy, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug related by the investigator.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of Id or IRd combinations.

10.1.8 Interim Analysis

An interim analysis will be conducted after the stage I (Ten (10) evaluable patients). If 3 or less patients in the arm demonstrate objective response, then the arm is closed and concluded with no potential better RR than the historical control RR of 30%. At least 4 objective responses are required to proceed to stage II accrual of 20 additional patients for a total of 30 patients per arm.

10.1.9 Early Stopping Rule

In this study, Grade 4 or greater nonhematological toxicity will be monitored starting from the first 15 response-evaluable patients and then every 5 response evaluable patients. If the stopping bounds of $\geq 5/15, \geq 6/20, \geq 7/25, \geq 8/30, \geq 9/35, \geq 10/40$, and $\geq 11/45$ have been achieved, accrual

to the study will be suspended to allow for investigation. After consideration by the study team (Millennium/Takeda clinician, study chair, statistician), a decision will be made as to whether accrual can be resumed.

The bounds are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rule is met, there is 80% probability that the true toxicity rate is greater than 18% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate. [31]

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected

transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

11.2 Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

AEs which are serious must be reported from the first dose of study drug through 30 days after administration of the last dost of ixazomib. Any SAE that occurs at any time after the first dose of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported. In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or inter-current illness.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported:

Fatal and Life Threatening SAEs within 24 hours of the investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 24 hours of the investigator's observation or awareness of the event

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Winship Cancer Institute at Emory University.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4.03 whenever possible.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

11.3 Procedures for AE and SAE Recording and Reporting

Reporting Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's research record and on the appropriate study-specific case report forms of the EDC. All AEs must be recorded in the participant's research record, stating the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study drug(s) and the adverse event.

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The investigator must evaluate all abnormal laboratory results to determine the clinical significance. If an abnormal result appears to be clinically significant, it must be considered to be an adverse event.

The descriptions and grading scales found in the CTEP Version 4.03 of the NCI CTCAE will be utilized for AE reporting. The CTEP Version 4.03 of the CTCAE is identified and located on the CTEP website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

11.4 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the study PI. All Serious Adverse Events (SAEs) that occur following the subject's first dose of study medication through 30 days of

discontinuation of dosing must be reported. In addition, any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure must be reported.

Each adverse event will be assessed to determine if it meets the criteria for SAE reporting. Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events as described below.

For participating subsites, adverse events collected at weekly treatment visits are to be entered into the EDC no later than 14 calendar days after data collection.

Subsites are not permitted to report directly to the coordinating center IRB or FDA. All external site SAEs are to be reported to the coordinating center multi-site's regulatory specialist. The coordinating center multi-site coordinator will facilitate submission of external site SAEs to the coordinating center IRB and FDA. All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the coordinating center principal investigator and coordinating center multi-site regulatory specialist within 24 hours of knowledge of the event using the PINR MMRC 060 Serious Adverse Event Report Form. Copies of de-identified source documentation pertaining to the SAE must be submitted to the coordinating center.

If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up form. All SAEs must be submitted to the local IRB per local IRB and institutional policy. Upon request of additional data or information that is deemed necessary must be reported to the coordinating center as soon as possible but no later than 5 calendar days.

11.5 Reporting to the MMRC Lead Investigator

11.5.1 Serious Adverse Event Reporting

When the Investigator or his/her designee becomes aware that an SAE has occurred, the Investigator must complete and submit a PINR MMRC 060 Serious Adverse Event Report Form,

which will be used as the primary method for SAE reporting to Winship Cancer Institute. All SAE reports that have the minimum data set for reporting should be submitted, even if only limited information is available. This must occur within 24 hours of learning of the occurrence, regardless of the relationship of the SAE to 'Study Drug.' In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

Follow-up reports must be submitted within 24 hours as additional information becomes available.

Investigators are responsible for notifying the Institutional Review Board (IRB) SAEs in accordance with local regulations.

Each site is responsible for reporting all SAEs, regardless of expectedness or causality to Winship Cancer Institute of Emory University within 24 hours of receiving the SAEs from investigator.

In addition, Winship Cancer Institute of Emory University will promptly provide MMRC Lead Investigator and other MMRC participating Investigators with adverse events that require expedited reporting to local IRBs.

Winship Cancer Institute of Emory University or the MMRC Lead Investigator may request additional source documentation pertaining to the SAE. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up report.

All serious adverse events that occur after the date of informed consent signature, during treatment occurring or within 30 days of the last administered dose of study drug must also be reported.

All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented in the paper PINR MMRC 060 Serious Adverse Event Report Form.

Within the following 24 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Information submitted in the paper PINR MMRC 060 Serious Adverse Event Report Form must be added to the EDC within 24 hours. Follow up reports must be submitted within 24 hours as additional information becomes available.

11.6 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported on the Adverse Event Case Report Form of the EDC, stating the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study and the adverse event.

11.7 Reporting to the Institutional Review Board (IRB)

Investigators should report adverse events to their respective IRB according to the local IRB policies and procedures in reporting adverse events.

11.8 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies occurring while the participant is on study drug orwithin 28 days of the participant's last dose of study drug should be reported immediately upon investigator's knowledge. If the participant is on study drug (Ixazomib and or lenalidomide, the drug(s) are to be discontinued immediately and the participant is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately of the Investigator's knowledge of the pregnancy. Reporting to Celgene as required by the Revlimid REMS ® program for patients taking lenalidomide. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the participant until completion of the pregnancy, and must report the outcome of the pregnancy (including notification of false-positive tests) within 24 hours of having knowledge of the event. Reporting to Celgene as required by the Revlimid REMS® program.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting SAEs (i.e., report the event within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported. Reporting to Celgene as required by the Revlimid REMS® program.

If the patient is found not to be pregnant, any determination regarding the participant's continued participation in the study will be determined by the Investigator.

A female partner of a male taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male participant should notify the investigator of his partner's pregnancy and her healthcare provider information. If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue ixazomib and lenalidomide (IRd treatment group).

12. ADMINISTRATIVE REQUIREMENTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure.

12.2 Data Quality Assurance

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Principal investigators will have access to all data upon entry in the EDC application. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to

the appropriate regulations.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

12.3 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

This study must have the approval of a properly constituted IRB or IEC. Before the investigational drug is shipped to the Site Investigator, the Site Investigator or designee will provide a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Site Investigator is also responsible for notifying their IRB/IEC of any significant adverse events that are serious, unanticipated and/or unexpected according to local IRB policies.

Millennium/Takeda will provide Investigators with any investigational new drug (IND) safety reports generated, changes to the Investigator's Brochure IB, and any safety updates. The Site Investigators are responsible notifying their IRB/IEC of any such updates in accordance to their IRB policies

The Lead Principal Investigator will initiate in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the IRB/IEC, together with a revised informed consent, if applicable. Written documentation of IRB/IEC approval must be received before the amendment is implemented. Upon completion of the trial, the Site Investigator must provide the IRB/IEC with a summary of the trial's outcome.

12.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of

obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the Site Investigator.

12.5 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from Millennium/Takeda or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The investigator/institution will permit direct access to source data and documents by the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

12.6 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from the investigators and Millennium/Takeda and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to Millennium/Takeda and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

Regulatory authorities, the IEC/IRB, and/or Millennium/ Takeda may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.7 Study Documentation and Archives

12.7.1 Source Documents

Source Documents are original documents, data, and records (e.g., medical records, data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.7.2 Case Report Form Completion

All data will be collecting using EDC system. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

12.7.3 Archival of Records

The Site Investigator must retain protocols, amendments, IRB/IEC approvals, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study for a period of 2 years after the investigation is discontinued.

12.8 Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6

months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

12.9 Study Monitoring and Data Collection for Participating sites

Following initiation of the study site, remote monitoring will be completed by the Winship DSMC and MSC. The Site Investigator will allocate sufficient time for the designated site staff to submit source documentation as required to complete remote monitoring.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.

- The reported data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, amendment(s), ICH GCP, FDA CFR, and any other applicable regulatory requirements.

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail.

Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Study updates will occur at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition, electronic copies will be sent via email to the principal investigators at each site.

12.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records for ixazomib indicating the drug's delivery date to the site,

inventory at the site, use by each patient, and amount returned to Millennium or a designee or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

12.11 Ixazomib Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium/Takeda Quality representative.

For Product Complaints,

Phone: 1-844-ONC-TKDA (1-844-662-8532)
E-mail: GlobalOncologyMedinfo@takeda.com
FAX: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium/Takeda.

12.12 Study Termination

This study may be prematurely terminated, if in the opinion of the investigator or Millennium if there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug.

13. INVESTIGATOR AGREEMENT

I have read Protocol Phase 2 Study of the Oral Form of ixazomib, a second-generation proteasome inhibitor, in combination with dexamethasone with or without lenalidomide in Adult patients with relapsed Multiple Myeloma.

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator printed name

_____ _____

Principal Investigator signature Date

_____

Investigational site or name of institution and location (printed)

14. REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29
2. Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. Haematologica. 2009;94(2):270-275.
3. Martinez-Lopez J, Blade J, Mateos MV, et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. Blood. 2011;118(3):529- 534.
4. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. Nature. 2011;471(7339):467-472.esponse in multiple myeloma after stem cell transplantation. Blood. 2011;118(3):529-534.
5. Gupta, N., et al., Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies. in 52nd ASH Annual Meeting and Exposition, 2010. **116**(21): p. abstr 1813.
6. Gupta, N., M. Saleh, and K. Venkatakrishnan. Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies in 53rd ASH Annual Meeting and Exposition. 2011. San Diego, CA; p. abstr 1433
7. Chow, L.Q., et al. MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated Phase 1 results in Head and Neck Symposium. 2012. Phoenix, AZ
8. Assouline, S., et al. Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a Phase 1 dose-escalation study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.
9. Lonial, S., et al. Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM) in ASCO Annual Meeting. 2012. Chicago, Illinois.
10. Kumar S, et al. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose-Escalation Study In 53rd ASH Annual Meeting and Exposition; 2011 10- 13 Dec; San Diego, CA; p. abstr 816..
11. Merlini, G., et al. MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia.
12. Kumar, S. et al. A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM). Lancet Oncology, 2014.15:1053-12.
13. Richardson, P.G., et al. MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts):

Evaluation of weekly and twice-weekly dosing in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.

14. San Miguel, J., et al. Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a Phase 1 study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.
15. Richardson P, Baz R, Wang L, Jakubowiak A, Berg D, Liu G, et al. Investigational Agent MLN9708, An Oral Proteasome Inhibitor, in Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (MM): Results From the Expansion Cohorts of a Phase 1 Dose-Escalation Study In: 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 301.
16. Lonial S, Baz R, Wang M, Talpaz M, Liu G, Berg D, et al. Phase I study of twice weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM). J Clin Oncol (ASCO Meeting Abstracts) 2012;30(15 suppl):abstr 8017.
17. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Berg D, et al. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose- Escalation Study In: 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 816.
18. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Liu G, et al. Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A Phase I study. Journal of Clinical Oncology 2012 ASCO Annual Meeting Proceedings 2012:Abstract 8034.
19. Kumar S, Niesvizky R, Berdeja J, Bensinger W, Zimmerman T, Berenson J, et al. Safety and Pharmacokinetics of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, Alone and in Combination. Clinical Lymphoma Myeloma and Leukemia 2013;13(Supplement 1):S154; abstr P-230
20. Common Terminology Criteria for Adverse Events (CTCAE). V.4.03
21. Kumar, S., Besinger W.I., Zimmerman, T.M., et al. Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in relapsed/refractory multiple myeloma – Results from a Phase 1 study. Blood 2014 Aug 14;124(7):1047-55
22. Richardson, P.G., Baz, R., Wang M., et al. Phase 1 study of twice-weekly dosing of investigational oral proteasome inhibitor MLN9708 in patients with relapsed and/or refractory multiple myeloma. Blood 2014 Aug 14;124(7):1038-46
23. Richardson, P.G., Hofmeister, C.C., Rosenbaum, C.A., et al. Twice Weekly Oral MLN9708 , An Investigational Proteasome Inhibitor, in Combination with Lenalidomide (Len) and Dexamethasone (Dex) in Patients (Pts) with newly diagnosed Multiple Myeloma(MM): Final Phase 1 results and Phase 2 Data. ASH 2013 Annual Meeting Abstract 535

15. APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

15.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Participant Signature: _____ Date: _____

15.3 International Myeloma Working Group Response Criteria[27]

Response[1]	*IMWG criteria*
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2–4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required

Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
MR	• 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M-protein by 50 to 89% which still exceeds 200 mg per 24 hr • In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive disease**	Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; All response categories (CR, sCR, VGPR, nad PD) require two consecutive assessments made at anytime before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.